ORIGINAL SUBMISSION

ToxStrategies

Innovative solutions
Sound science

March 13, 2015

Office of Food Additive Safety (HFS-200)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
College Park, MD 20740-3835

Subject: GRAS Notification – Oat-Derived Protein (PrOatein®)

Dear Sir:

On behalf of Tate & Lyle, ToxStrategies, Inc. (its agent) is submitting for FDA review Form 3667 and three copies of the notification as required. The enclosed document provides notice of a claim that the food ingredient described in the enclosed notification is exempt from the premarket approval requirement of the Federal Food, Drug, and Cosmetic Act because it has been determined to be generally recognized as safe (GRAS), based on scientific procedures, for addition to specified foods as a source of dietary protein.

If you have any questions or require additional information, please do not hesitate to contact me at 630-352-0303, or dschmitt@toxstrategies.com.

Sincerely,

(b) (6)

Don Schmitt, M.P.H.
Senior Managing Scientist

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

# GENERALLY RECOGNIZED AS SAFE *(GRAS)* NOTICE

Form Approved: OMB No. 0910-0342; Expiration Date: 02/29/2016
*(See last page for OMB Statement)*

**FDA USE ONLY**

| GRN NUMBER | DATE OF RECEIPT |
|---|---|
| ESTIMATED DAILY INTAKE | INTENDED USE FOR INTERNET |
| NAME FOR INTERNET | |
| KEYWORDS | |

RECEIVED
MAR 17 2015
OFFICE OF FOOD ADDITIVE SAFETY

Transmit completed form and attachments electronically via the Electronic Submission Gateway *(see instructions)*; OR Transmit completed form and attachments in paper format or on physical media to: Office of Food Additive Safety *(HFS-200)*, Center for Food Safety and Applied Nutrition, Food and Drug Administration, 5100 Paint Branch Pkwy., College Park, MD 20740-3835.

## PART I – INTRODUCTORY INFORMATION ABOUT THE SUBMISSION

1. Type of Submission *(Check one)*

☒ New ☐ Amendment to GRN No. _____ ☐ Supplement to GRN No. _____

2. ☐ All electronic files included in this submission have been checked and found to be virus free. *(Check box to verify)*

3a. For New Submissions Only: Most recent presubmission meeting *(if any)* with FDA on the subject substance *(yyyy/mm/dd)*: _____

3b. For Amendments or Supplements: Is your amendment or supplement submitted in response to a communication from FDA? *(Check one)* ☐ Yes ☐ No If yes, enter the date of communication *(yyyy/mm/dd)*: _____

## PART II – INFORMATION ABOUT THE NOTIFIER

**1a. Notifier**

| Name of Contact Person | Position |
|---|---|
| Ms. Lore Kolberg | Director, Regulatory Affairs |

Company *(if applicable)*: Tate & Lyle

Mailing Address *(number and street)*: 5450 Prairie Stone Parkway

| City | State or Province | Zip Code/Postal Code | Country |
|---|---|---|---|
| Hoffman Estates | Illinois | 60192 | United States of America |

| Telephone Number | Fax Number | E-Mail Address |
|---|---|---|
| 847-396-7608 | | Lore.Kolberg@tateandlyle.com |

**1b. Agent or Attorney *(if applicable)***

| Name of Contact Person | Position |
|---|---|
| Doanld F. Schmitt | Senior Managing Scientist |

Company *(if applicable)*: ToxStrategies, Inc.

Mailing Address *(number and street)*: 739 Thornapple Drive

| City | State or Province | Zip Code/Postal Code | Country |
|---|---|---|---|
| Naperville | Illinois | 60540 | United States of America |

| Telephone Number | Fax Number | E-Mail Address |
|---|---|---|
| 630-352-0303 | | dschmitt@toxstrategies.com |

## PART III – GENERAL ADMINISTRATIVE INFORMATION

1. Name of Substance

Oat protein

2. Submission Format: *(Check appropriate box(es))*

☐ Electronic Submission Gateway

☐ Electronic files on physical media with paper signature page

☒ Paper

If applicable give number and type of physical media

3. For paper submissions only:

Number of volumes _____

Total number of pages _____

4. Does this submission incorporate any information in FDA's files by reference? *(Check one)*

☒ Yes *(Proceed to Item 5)* ☐ No *(Proceed to Item 6)*

5. The submission incorporates by reference information from a previous submission to FDA as indicated below *(Check all that apply)*

☒ a) GRAS Notice No. GRN 26

☐ b) GRAS Affirmation Petition No. GRP _____

☐ c) Food Additive Petition No. FAP _____

☐ d) Food Master File No. FMF _____

☐ e) Other or Additional *(describe or enter information as above)* GRNs 37, 182, 327, 386, 437, and 447

6. Statutory basis for determination of GRAS status *(Check one)*

☒ Scientific Procedures *(21 CFR 170.30(b))* ☐ Experience based on common use in food *(21 CFR 170.30(c))*

7. Does the submission (including information that you are incorporating by reference) contain information that you view as trade secret or as confidential commercial or financial information?

☐ Yes *(Proceed to Item 8)*

☒ No *(Proceed to Part IV)*

8. Have you designated information in your submission that you view as trade secret or as confidential commercial or financial information *(Check all that apply)*

☐ Yes, see attached Designation of Confidential Information

☐ Yes, information is designated at the place where it occurs in the submission

☐ No

9. Have you attached a redacted copy of some or all of the submission? *(Check one)*

☐ Yes, a redacted copy of the complete submission

☐ Yes, a redacted copy of part(s) of the submission

☐ No

## PART IV – INTENDED USE

1. Describe the intended use of the notified substance including the foods in which the substance will be used, the levels of use in such foods, the purpose for which the substance will be used, and any special population that will consume the substance *(e.g., when a substance would be an ingredient in infant formula, identify infants as a special population)*.

Oat-derived protein is intended for use as a source of protein for enrichment of foods. It will be added to processed foods at per serving levels in an identical fashion (technical function and amount) to those described in other GRAS Notification submissions to the U.S. FDA for other protein sources such as canola protein isolates (all received no objection letters; GRNs 327 and 386). Example food categories include bakery products; snack foods; dairy products; processed meat products; beverages, soups, and nutritional beverages; dry instant milkshake and protein drinks; instant powdered nutritional beverages; vegetarian food products and meat analogues; and meal replacement/nutritional bars.

2. Does the intended use of the notified substance include any use in meat, meat food product, poultry product, or egg product? *(Check one)*

☒ Yes ☐ No

## PART V – IDENTITY

**1. Information about the Identity of the Substance**

| | Name of Substance[1] | Registry Used *(CAS, EC)* | Registry No.[2] | Biological Source *(if applicable)* | Substance Category *(FOR FDA USE ONLY)* |
|---|---|---|---|---|---|
| 1 | Oat protein(s) | CAS | 134134-87-5 | Oats | |
| 2 | | | | | |
| 3 | | | | | |

[1] Include chemical name or common name. Put synonyms *(whether chemical name, other scientific name, or common name)* for each respective item (1 - 3) in Item 3 of Part V *(synonyms)*

[2] Registry used e.g., CAS *(Chemical Abstracts Service)* and EC *(Refers to Enzyme Commission of the International Union of Biochemistry (IUB), now carried out by the Nomenclature Committee of the International Union of Biochemistry and Molecular Biology (IUBMB))*

**2. Description**

Provide additional information to identify the notified substance*(s)*, which may include chemical formula*(s)*, empirical formula*(s)*, structural formula*(s)*, quantitative composition, characteristic properties *(such as molecular weight(s))*, and general composition of the substance. For substances from biological sources, you should include scientific information sufficient to identify the source *(e.g., genus, species, variety, strain, part of a plant source (such as roots or leaves), and organ or tissue of an animal source)*, and include any known toxicants that could be in the source.

Oat- derived protein is manufactured to meet the specifications on page 12 in Table 1.
The oat protein product composition is provided on pages 8-10 .

**3. Synonyms**

Provide as available or relevant:

| | |
|---|---|
| 1 | Protein derived from oat bran |
| 2 | PrOatein® |
| 3 | |

## PART VI – OTHER ELEMENTS IN YOUR GRAS NOTICE

*(check list to help ensure your submission is complete – check all that apply)*

- ☒ Any additional information about identity not covered in Part V of this form
- ☒ Method of Manufacture
- ☒ Specifications for food-grade material
- ☒ Information about dietary exposure
- ☒ Information about any self-limiting levels of use *(which may include a statement that the intended use of the notified substance is not-self-limiting)*
- ☐ Use in food before 1958 *(which may include a statement that there is no information about use of the notified substance in food prior to 1958)*
- ☒ Comprehensive discussion of the basis for the determination of GRAS status
- ☒ Bibliography

**Other Information**

Did you include any other information that you want FDA to consider in evaluating your GRAS notice?

☒ Yes ☐ No

Did you include this other information in the list of attachments?

☒ Yes ☐ No

## PART VII – SIGNATURE

1. The undersigned is informing FDA that Tate & Lyle *(name of notifier)*

has concluded that the intended use(s) of Oat protein *(name of notified substance)*

described on this form, as discussed in the attached notice, is (are) exempt from the premarket approval requirements of section 409 of the Federal Food, Drug, and Cosmetic Act because the intended use(s) is (are) generally recognized as safe.

2. ☒ Tate & Lyle *(name of notifier)* agrees to make the data and information that are the basis for the determination of GRAS status available to FDA if FDA asks to see them.

Tate & Lyle *(name of notifier)* agrees to allow FDA to review and copy these data and information during customary business hours at the following location if FDA asks to do so.

5450 Prairie Stone Parkway, Hoffman Estates, Illinois 60192 *(address of notifier or other location)*

Tate & Lyle *(name of notifier)* agrees to send these data and information to FDA if FDA asks to do so.

**OR**

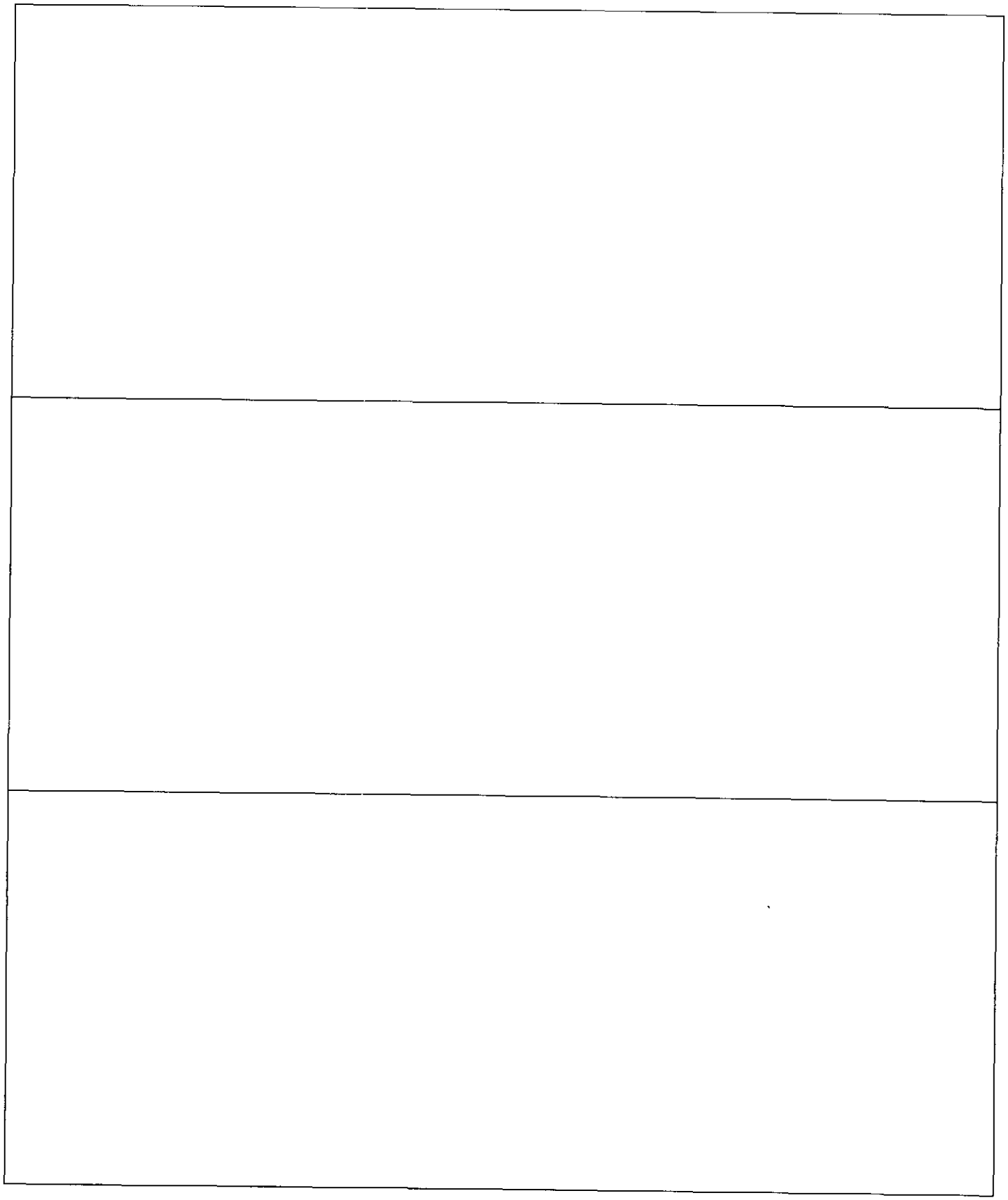
☐ The complete record that supports the determination of GRAS status is available to FDA in the submitted notice and in GRP No. ---------- *(GRAS Affirmation Petition No.)*

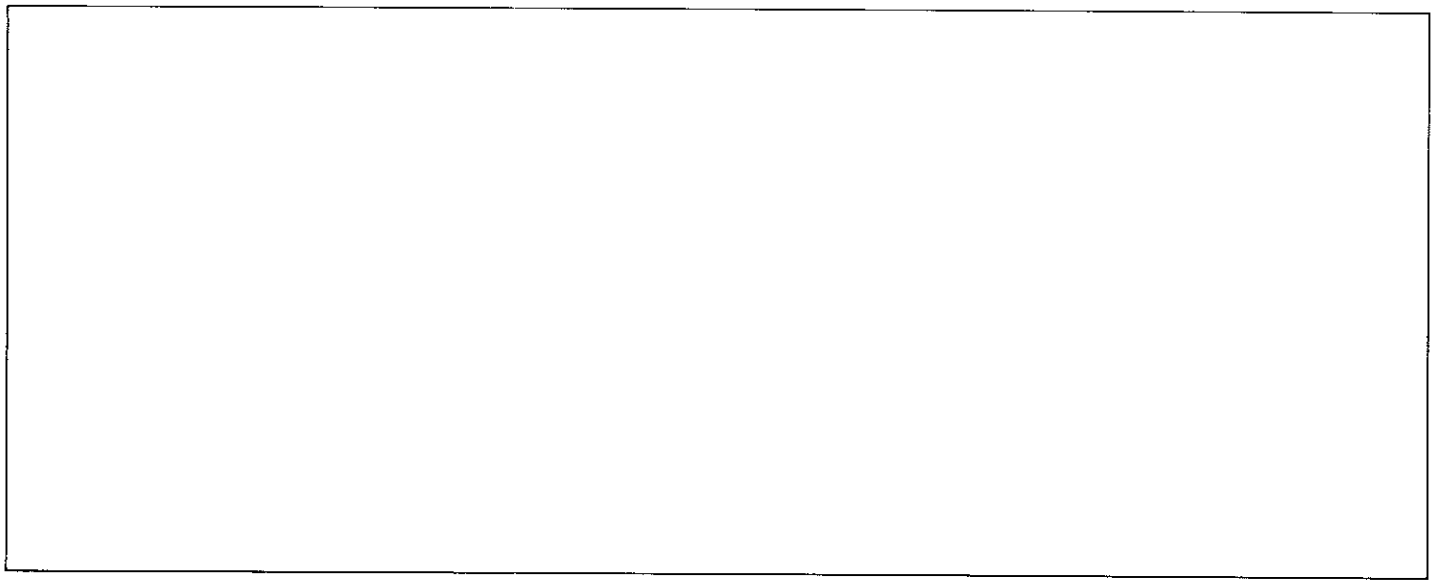
| 3. Signature of Responsible Official, Agent, or Attorney | Printed Name and Title | Date (mm/dd/yyyy) |
|---|---|---|
| (b) (6) | onald F. Schmitt, Senior Managing Scientist | 03/13/2015 |

## PART VIII – LIST OF ATTACHMENTS

List your attached files or documents containing your submission, forms, amendments or supplements, and other pertinent information. Clearly identify the attachment with appropriate descriptive file names (or titles for paper documents), preferably as suggested in the guidance associated with this form. Number your attachments consecutively. When submitting paper documents, enter the inclusive page numbers of each portion of the document below.

| Attachment Number | Attachment Name | Folder Location (select from menu) (Page Number(s) for paper Copy Only) |
|---|---|---|
| | Appendix A - Certificates of Analysis - Characterization | pp. 43-59 |
| | Appendix B - Technical Product Data Sheet | pp. 60-61 |
| | Appendix C - T&L Analytical Risk Assessment | pp. 62-63 |
| | Appendix D - Stability Test Results | pp. 64-65 |
| | Exhibit 1 - Report of the Expert Panel | pp. 66-74 |
| | | |
| | | |
| | | |
| | | |





# GRAS Determination of Oat Protein for Use in Food

**SUBMITTED BY:**

Tate & Lyle
5450 Prairie Stone Parkway
Hoffman Estates, IL 60192

**SUBMITTED TO:**

U.S. Food and Drug Administration
Center for Food Safety and Applied Nutrition
Office of Food Additive Safety
HFS-200
5100 Paint Branch Parkway
College Park MD 20740-3835

**CONTACT FOR TECHNICAL OR OTHER INFORMATION**

Donald F. Schmitt, MPH
ToxStrategies, Inc.
739 Thornapple Drive
Naperville, IL 60540

March 5, 2015

## Table of Contents

## List of Acronyms

| | |
|---|---|
| ACH | alcalase |
| ADME | absorption, distribution, metabolism, and excretion |
| bw | body weight |
| C | centigrade |
| CD | celiac disease |
| cGMP | current Good Manufacturing Practice |
| CAS | Chemical Abstracts Service |
| CDC | Centers for Disease Control |
| CFR | Code of Federal Regulations |
| CI | confidence interval |
| COA | certificate of analysis |
| dL | deciliter |
| DON | deoxynivalenol |
| DPPH | 2,2'-diphenyl-2-picrylhydrazyl |
| DRV | dietary reference value |
| EDI | estimated daily intake |
| FDA | Food and Drug Administration |
| G | gram |
| GFD | gluten-free diet |
| GI | gastrointestinal |
| GLP | Good Laboratory Practice |
| GMP | Good Manufacturing Practice |
| GRAS | Generally Recognized as Safe |
| GRNs | Generally Recognized as Safe Notifications |
| IOM | Institute of Medicine |
| kDa | kilodalton |
| kg | kilogram |
| L | liter |
| LDL | low-density lipoprotein |
| mg | milligram |
| mL | milliliter |
| MoAb | monoclonal antibody |
| mRNA | messenger ribonucleic acid |
| ppm | parts per million |
| RDA | recommended dietary allowance |
| TG2 | transglutaminase |
| TPH | protein hydrolysates from trypsin |
| US | United States |
| USDA | United States Department of Agriculture |
| WHO | World Health Organization |
| wk | week |



3

# 1.0. GRAS Exemption Claim

## A. Name and Address of Notifier

Tate & Lyle, through its agent ToxStrategies, Inc., hereby notifies the Food and Drug Administration that the use of the identified oat protein product described below and which meets the specifications described herein is exempt from pre-market approval requirements of the Federal Food, Drug, and Cosmetic Act because Tate & Lyle has determined that such use is generally recognized as safe (GRAS) through scientific procedures.

(b) (6)

03/13/15

Donald F. Schmitt, M.P.H.
Senior Managing Scientist
ToxStrategies, Inc.
Agent for Tate & Lyle

Date

## B. Name of GRAS Substance

The name of the substance that is the subject of this GRAS determination is PrOatein® Oat Protein, an oat protein prepared from oat bran.

## C. Intended Use in Food

Oat-derived protein is intended for use as a source of protein for enrichment of foods. It will be added to processed foods at per serving levels in an identical fashion (technical function and amount) to those described in other GRAS Notification submissions to the U.S. FDA for other protein sources such as canola protein isolates (all received no objection letters; GRNs 327 and 386). Example food categories include bakery products; snack foods; dairy products; processed meat products; beverages, soups, and nutritional beverages; dry instant milkshake and protein drinks; instant powdered nutritional beverages; vegetarian food products and meat analogues; and meal replacement/nutritional bars. The amount used will not exceed the amount reasonably required to accomplish its intended technical effect.

## D. Basis for GRAS Determination

This Assessment documents the evidence of the safety and the "Generally Recognized As Safe" (GRAS) status of the proposed uses of Tate & Lyle's oat-derived protein product (PrOatein®). It consists of an evaluation of the safety and the GRAS status of the proposed uses of this ingredient, and the conclusion by a panel of experts (Expert Panel) qualified by scientific training and experience to evaluate the safety of substances added to food that the proposed uses of Tate& Lyle's oat protein ingredient are safe and GRAS as determined by scientific procedures.

Tate & Lyle's GRAS determination for the intended use of oat-derived protein is based on scientific procedures as described under 21 CFR § 170.30(b). The intended use of the oat protein product has been determined to be safe and GRAS, and the safety of intake exposure under the proposed conditions of use is based on knowledge and information that is both publicly available and widely accepted by experts qualified by scientific training and experience to evaluate the safety of substances in food. The publicly available safety data combined with the widely disseminated knowledge concerning the chemistry of protein from various sources such as oats, potatoes, wheat, canola, and whey combined with the long history of approval/use of such ingredients provide a sufficient basis for an assessment of the safety of oat-derived protein for the uses proposed herein.

To date, the FDA has issued "no questions" letters in response to Generally Recognized As Safe (GRAS) Notifications (GRNs) on protein concentrates and protein isolates from numerous plant and cereal grain-based sources (GRN No. 26, isolated wheat protein, 1999; GRN No. 37, whey protein isolate, 2000; GRN No. 182, hydrolyzed wheat gluten isolate and pea protein isolate, 2006; GRN No. 327, cruciferin-rich canola/rapeseed protein isolate and napin-rich canola/rapeseed protein isolate, 2010; GRN No. 386, canola protein isolate and hydrolyzed canola protein isolate, 2011; GRN No. 447, potato protein isolates, 2013). In addition to containing reviews of the published safety information, the GRNs included expert panel reports that reviewed and discussed in detail the metabolism, toxicology, and human health and safety data for protein and protein concentrates/isolates. Based on these GRAS notifications, FDA currently permits the use of protein preparations from a variety of plant-based sources at the use-levels indicated in the notifications.

There is common knowledge of a long history of human consumption of oats. As noted in the GRNs cited above, there is also a long history of safe use of plant-based protein concentrates and isolates in processed food. The focus of this GRAS determination is for an identical use of oat-derived protein, as an alternative source of dietary protein, as for currently available protein sources added to processed foods. There is a long history of the safe use of oats and products derived from oats. Furthermore, other natural sources of protein concentrates, such as canola, potato, and wheat, have been safely consumed for years. Tate & Lyle currently markets oat protein (PrOatein®) outside of the U.S. However, oat protein products are currently marketed in the U.S. (e.g., 55Oat Protein, Oat Tech, Inc.). While there is a noted lack of published safety studies on oat protein concentrates, the safety section that follows describes numerous animal and human safety studies of oats and other GRAS-notified protein sources currently added to processed foods.

Epidemiological studies and clinical trials have consistently revealed the cardiovascular benefits of oat consumption from its hypocholesterolemic effects. In 1997, the FDA approved a health claim for the association between oat consumption and coronary heart disease (Katz, 2001; FDA, 1997).

Protein is found throughout the body, in muscle, bone, skin, hair, and virtually every body part or tissue. At least 10,000 different proteins are found in the body. Proteins are made up of amino acids that act as building blocks to make all types of protein. Some amino acids cannot be made by the body and therefore must be provided by the diet (i.e., essential amino acids). While animal sources of protein tend to deliver all the amino acids the body requires for proper nutrition leading to normal or nominal nutriture, other protein sources also deliver most of these same essential amino acids and have become an important source of added protein in processed food. Current plant and cereal grain sources of protein include peas, lentils, soy, canola, rice, chickpeas, beans, wheat, and potato.

FDA has established a daily reference value (DRV) for protein of 50 g/day for adults and children four or more years of age. The Institute of Medicine (IOM, 2005) has established a Recommended Dietary Allowance (RDA) of 56 g/day for adult males and 46 g/day for adult females.

To date, FDA has reviewed extensive published information and data as part of GRAS notifications for animal and plant-based protein isolates and concentrates and subsequently issued "no questions letters" (e.g., GRN No. 26 (isolated wheat protein); GRN No. 37 (whey protein isolate and dairy product solids); GRN No. 168 (poultry protein); GRN No. 182 (hydrolyzed wheat gluten isolate; pea protein isolate); GRN No. 313 (beef protein); GRN No. 314 (pork protein); GRN 327 (canola/rapeseed protein isolates); GRN 386 (canola protein isolate and hydrolyzed canola protein isolate); GRN No. 447 (potato protein isolates)). No recent studies raising any new safety concerns concerning protein or protein isolates and their addition to processed foods have appeared in the published literature subsequent to these evaluations.

Given that oat protein (PrOatein®) meets the proposed specifications contained herein, the safe use of oat protein is justified by scientific procedures. In addition, the publicly available scientific literature is sufficient to support the safety and GRAS status of the proposed oat protein product. Therefore, since this safety evaluation was based on generally available and widely accepted data and information, it also satisfies the so-called "common knowledge" element of a GRAS determination.

Determination of the safety and GRAS status of this oat-derived protein product described above for direct addition to food under its intended conditions of use was made through deliberation of an Expert Panel consisting of Michael Carakostas, DVM, Ph.D., Carol A. Knight, Ph.D., and Stanley M. Tarka, Jr., Ph.D, who reviewed a dossier prepared by ToxStrategies as well as other information available to them. These individuals are qualified by scientific training and experience to evaluate the safety of food and food ingredients. They individually and collectively critically evaluated published data and information pertinent to the safety of oat-derived protein, and unanimously concluded that the intended use of oat protein in food, produced consistent with cGMP and meeting appropriate specifications as delineated above, is "generally recognized as safe" ("GRAS") based on scientific procedures.

## E. Availability of Information

The data and information that serve as the basis for this GRAS determination, as well any information that has become available since the GRAS determination, will be sent to the FDA upon request, or are available for the FDA's review and copying at reasonable times from ToxStrategies, Inc., Naperville, IL.



7

## 2.0 Description of Substance

### A. Identity

Oat protein (PrOatein® Oat Protein) is a natural protein concentrate derived from oat bran and is rich in essential amino acids.

### B. Common Name

Oat protein(s).

### C. CAS Registry Number

The Chemical Abstracts Service (CAS) Registry Number for oat proteins is 134134-87-5.

### D. Trade Names

The trade name of Tate & Lyle's oat protein is PrOatein® or PrOatein® Oat Protein.

### E. Chemical/Structural Formulas

Oat protein (PrOatein®) is a protein concentrate, prepared from oat bran and rich in oat protein, typically containing 52-56% protein (dry basis). It also contains oat oil and oat maltodextrins (approved in 21 CFR §184.1444) both of which occur naturally in the oat, as well as a small amount of minerals and β-glucan (see Figure 1 below).

### F. Oat Protein Composition

Among cereal grains, oats are considered unique due to their relatively high protein content and distinct protein composition. As indicated above and in Figure 1 below, PrOatein® contains oat oil. The PrOatein® oil fraction (16-18% of the PrOatein® product) is comprised of approximately 42% linoleic acid, 36%, oleic acid, 16% palmitic acid, 2% α-linolenic acid, and 4% other fatty acids (C20 - 24) normally found in oats. The high concentration of unsaturated fatty acids (namely the monounsaturated oleic acid, along with the high amount of monounsaturated and polyunsaturated fatty acids (mainly omega-6) provides a desirable nutritional profile. Oat protein is also rich in essential amino acids (including leucine, isoleucine and lysine). The composition and amino acid profile of PrOatein® Oat Protein is illustrated in the following two figures. The amino acid profile of a representative batch of PrOatein® (i.e., Batch No. 1334) can be found in Appendix A.

**Figure 1. Oat Protein Composition and Amino Acid Profile**

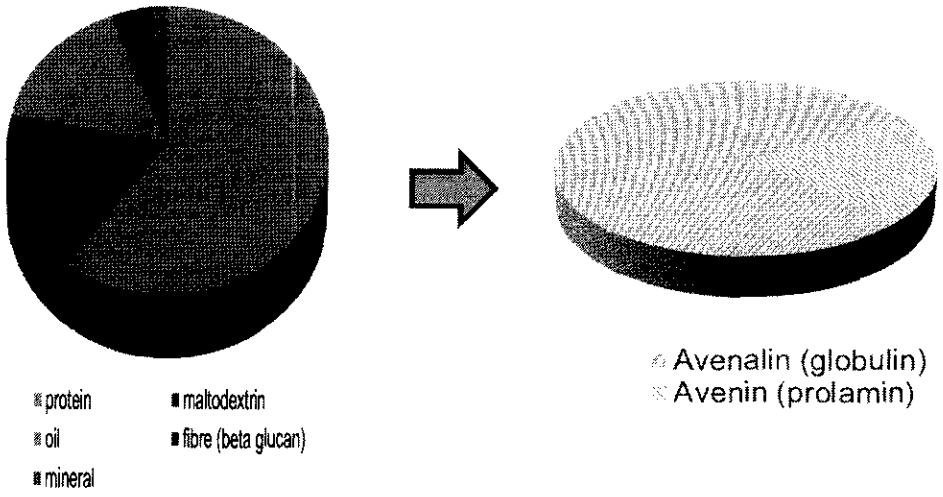
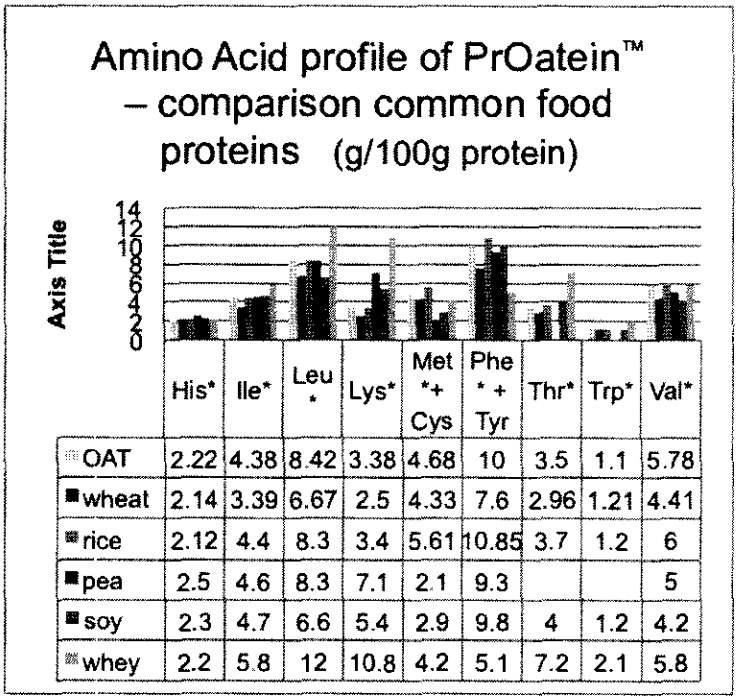



Figure 2. Amino Acid Profile

| | 2012 | 2013 |
|---|---|---|
| Ala | 4,37 | 4,39 |
| Arg' | 7,17 | 7,08 |
| Asp' | 7,48 | 7,60 |
| Cys' | 2,45 | 2,12 |
| Glu | 22,50 | 22,70 |
| Gly' | 4,13 | 4,21 |
| His* | 2,22 | 2,20 |
| Ile* | 4,38 | 4,62 |
| Leu* | 8,42 | 8,05 |
| Lys* | 3,38 | 3,42 |
| Met* | 2,23 | 1,79 |
| Phe* | 5,95 | 5,77 |
| Pro' | 5,57 | 5,35 |
| Ser' | 3,98 | 4,07 |
| Thr* | 3,22 | 3,01 |
| Trp* | 1,1 | |
| Tyr' | 4,05 | 3,87 |
| Val* | 5,78 | 6,08 |




| | His* | Ile* | Leu* | Lys* | Met*+ Cys | Phe* + Tyr | Thr* | Trp* | Val* |
|---|---|---|---|---|---|---|---|---|---|
| OAT | 2.22 | 4.38 | 8.42 | 3.38 | 4.68 | 10 | 3.5 | 1.1 | 5.78 |
| wheat | 2.14 | 3.39 | 6.67 | 2.5 | 4.33 | 7.6 | 2.96 | 1.21 | 4.41 |
| rice | 2.12 | 4.4 | 8.3 | 3.4 | 5.61 | 10.85 | 3.7 | 1.2 | 6 |
| pea | 2.5 | 4.6 | 8.3 | 7.1 | 2.1 | 9.3 | | | 5 |
| soy | 2.3 | 4.7 | 6.6 | 5.4 | 2.9 | 9.8 | 4 | 1.2 | 4.2 |
| whey | 2.2 | 5.8 | 12 | 10.8 | 4.2 | 5.1 | 7.2 | 2.1 | 5.8 |

*Method ISO 13903:2005 – Values +/- 8% EUROFINS Sweden AB*

Oats are the only cereal containing the globulin avenalin, as the major storage protein. Oat protein is nearly equivalent in quality to soy protein, which World Health

Organization research has shown to be equivalent to meat, milk, and egg protein. The protein content of the hull-less oat kernel (groat) ranges from 15 to 20%, the highest among cereals. As summarized above, compared to other grains, oats contain a favorable ratio of lipids and contain unsaturated fats, including the essential fatty acid linoleic acid. On a per gram basis, oats have higher concentrations of protein, fat, calcium, iron, magnesium, zinc, copper, manganese, thiamin, folacin, and vitamin E than other whole grains, such as wheat, corn, rice, barley, and rye. (http://www.quakeroats.com/libraries/pdf/oa®eal_for_children_and_toddlers.sflb.ashx)

Oats have been recognized for superior nutritional value because of the high percentage of protein as well as the superior amino acid balance versus other grains. Oats also contain several antioxidant phytonutrients including vitamin E tocols, caffeic and ferulic acids, flavonoid and nonflavonoid phenolics including a group of novel antioxidants – avenanthramides. (http://www.quakeroats.com/libraries/pdf/oa®eal_for_children_and_toddlers.sflb.ashx)

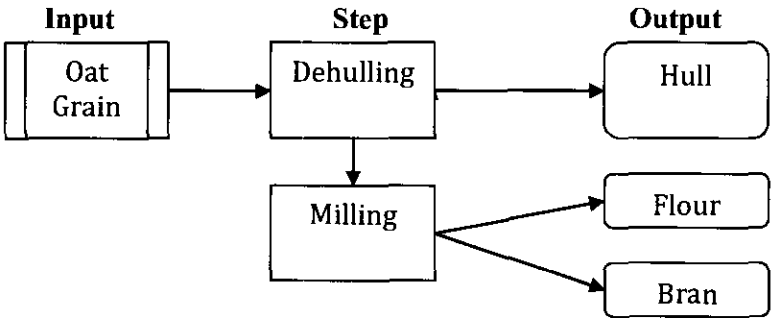
The protein fraction itself (as demonstrated in Figure 1 above), is composed of mainly globulin (avenalin) and much less prolamin (avenin). Oat protein and PrOatein® contains less prolamin than typical cereal storage proteins (e.g., wheat, rye, barley), which results in better digestibility than proteins with higher prolamin content. It should also be noted that the prolamin fraction does not contain gluten. Overall, oats provide proteins with high nutritive quality and with digestibility greater than 90%, biological value around 75% and net protein utilization of 70%. (http://www.oatsandhealth.org/composition-oats-and-health-27; http://www.oatsandhealth.org/composition-oats-and-health-27/oat-protein)

## G. Manufacturing Process

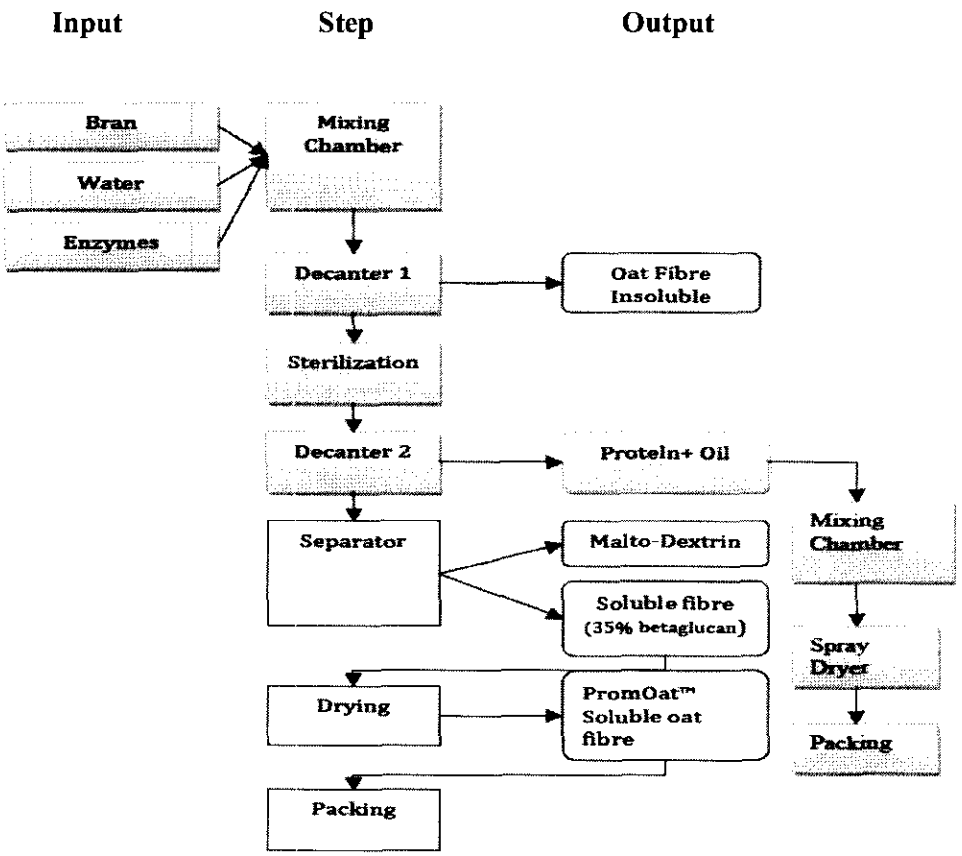
Tate & Lyle's PrOatein® product that is the subject of this GRAS determination is manufactured in a two-step process following current Good Manufacturing Practice (cGMP) for food (21 CFR Part 110), without the use of chemicals or solvents and it does not contain additives or preservatives. The first-step is a dry mill process in which the oat grain is dehulled (husk and most of endosperm separated) and milled to specifications. The final output of the dry milling process is oat bran, which is employed in the second processing step, a wet process. In the wet fractionation process, the oat bran is mixed with water and food use-approved enzymes from non-GMOs (genetically modified organisms) at specified temperatures. The mixture is passed through physical separation procedures and sterilized. The process output provides insoluble fiber, protein, oat oil, maltodextrin (approved in 21 CFR §184.1444), and oat soluble fiber rich in β-glucan, all of which can be supplied as dry products (see Step 2 below).

A flow diagram of Tate & Lyle's manufacturing process can be found below.

**Step 1. Dry Process**




**Step 2. Wet Process**




Reagents/processing aids used in the manufacture of oat protein are limited to water and the enzyme alpha-amylase, which is commonly used in food ingredient manufacturing processes. No chemical processing aids are employed in Tate &



11

Lyle's manufacturing process. The alpha-amylase enzyme preparation employed in the process is GRAS per 21 CFR §184.1012, complies with Food Chemicals Codex specifications, and is used at levels not to exceed current good manufacturing practice.

## H. Product Specifications

Food grade specifications for Tate & Lyle's PrOatein® Oat Protein are presented in Table 1. The typical protein content of PrOatein® is 52-56% on a dry matter basis. PrOatein® is a fine, beige-colored powder. Analytical results from three non-consecutive lots are provided in Appendix A (NOTE: Eurofins batch analysis for protein content is on an "as is" basis, not a dry matter basis as are the Tate & Lyle COAs). A comparison of three non-consecutive lots of PrOatein® to the specifications below can be found in Table 2.

### Table 1. Specifications for Oat Protein (PrOatein®)

| Parameter (Assay Method) | Specification |
|---|---|
| **Physical Characteristics** | |
| Appearance (Visual) | Fine, beige-colored powder |
| Moisture (IDF Standard 4A 1982) | Typically, 2-5% on a dry basis |
| Protein (IDF 20B 1993) | 52-56%, on a dry basis |
| **Heavy Metals*** | |
| Lead (NMKL No 161 1998) | ≤ 0.05 ppm |
| Arsenic (NMKL No 161 1998) | ≤ 0.1 ppm |
| Cadmium (NMKL No 161 1998) | ≤ 0.2 ppm |
| Mercury (NMKL No 161 1998) | ≤ 0.05 ppm |
| **Microbiological Analyses** | |
| Total plate count (NMKL No 86 1999) | <10,000 cfu/g |
| Enterobacteriaceae (NMKL No 144 2000) | <10 cfu/g |
| *Staphylococcus aureus* (NMKL No 66, 3 ed, 1999 modified) | <20 cfu/g |
| Yeasts (IDF 94B; 1990 modified) | <100 cfu/g |
| Molds (IDF 94B; 1990 modified) | <100 cfu/g |
| *Salmonella* (NMKL No 71, 5 ed, modified) | Negative/25g |
| *E.coli* (NMKL No 125, 3 ed, 1996) | Negative |

* It should be noted that heavy metals levels are not routinely reported on COAs (see Appendix A), but are documented in routinely conducted analytical reports which are also included in Appendix A.

## Table 2. Analytical Results for 3 Lots of Oat Protein (PrOatein®)

| Specification | | Lot No. 1332 | Lot No. 1411 | Lot No. 1413 |
|---|---|---|---|---|
| Protein | 52-56%, on a dry basis | 52.9 | 55.0 | 56.0 |
| Moisture | 3-6%, on a dry basis | 4.2 | 3.3 | 4.5 |
| **Heavy Metals*** | | | | |
| Lead | ≤ 0.1 ppm | <0.020 | <0.020 | <0.020 |
| Arsenic | ≤ 0.1 ppm | <0.050 | <0.050 | <0.050 |
| Cadmium | ≤ 0.2 ppm | 0.052 | 0.11 | 0.059 |
| Mercury | ≤ 0.1 ppm | <0.020 | <0.020 | <0.020 |
| **Microbiological Analyses** | | | | |
| Total plate count | <10,000 cfu/g | <1000 | <1000 | <1000 |
| Enterobacteriaceae | <10 cfu/g | <10 | <10 | <10 |
| *Staphylococcus aureus* | <20 cfu/g | <20 | <20 | <20 |
| Yeasts | <100 cfu/g | <20 | <20 | <20 |
| Molds | <100 cfu/g | <20 | <60 | <20 |
| *Salmonella* | Negative/25g | Neg/25g | Neg/25g | Neg/25g |
| *E.coli* | Negative | Negative | Negative | Negative |

* Heavy metals levels are not routinely reported on COAs (see Appendix A), but are documented in routinely conducted analytical reports which are also included in Appendix A.

Typical compositional and nutritional analyses of Tate & Lyle's PrOatein® product containing 52-56% protein are presented in Table 3.

## Table 3. Nutritional Analyses of PrOatein®

| Nutrient | Amount |
|---|---|
| Calories (kcal/100g) | 445 |
| Protein (g/100g) | 54 |
| Total fat (g/100g) | 17 |
| Saturated fat (g/100g) | 3 |

| | |
|---|---|
| Carbohydrate (oat maltodextrins) (g/100g) | 18 |
| Fiber (oat beta-glucan soluble fiber) (g/100g) | 2 |
| Sugars (g/100g) | 0.4 |
| Iron (mg/100g) | 400 |
| Sodium (mg/100g) | 20 |
| Calcium (g/100g) | 12 |

A COA and oat supplier (Lantmannen, Stockholm, Sweden) declaration of regulatory compliance on the starting material (food grade oats) is included in Appendix A. The supplier of the starting oats product regularly analyzes their oats for the presence of mycotoxins and guarantees that the oats meet the limits set for mycotoxins (e.g., aflatoxins, deoxynivalenol (DON), ochratoxin) and other foodstuff contaminants prescribed in EU regulation 1881/2006. It should be noted that the supplier Lantmannen was audited for GMP compliance by FDA in 2014. Compliance with the aforementioned EU regulations also results in compliance with FDA requirements regarding the presence of mycotoxins such as aflatoxins (20 ppb), DON (1 ppm) and ochratoxin A (3 ppb) in foodstuffs like oats. In addition, incoming oats are tested by plant operators for appearance, smell, color, density, and percent of other grains as well as other possible contaminants. Tate & Lyle analytical labs also analyze for dry matter and protein content. One batch of PrOatein® is the total production during one week. Therefore, given down time for plant maintenance, it is expected that approximately 50 batches of PrOatein® will be produced yearly. Based on an internal risk analysis on the raw material and final PrOatein® product (see Appendix C), Tate & Lyle has determined that a minimum of twice yearly analysis of the finished product is justified. The analyses include mycotoxins, pesticides, heavy metals, minerals, and other parameters as indicated in the attached COAs.

The analytical (chemical and microbiological) results for PrOatein® summarized in the above tables and included in the COAs and Technical Data Sheets in Appendices A and B confirm that the finished product meets the analytical specifications and demonstrates that the PrOatein® manufacturing process results in a consistently reproducible product, and confirms the lack of impurities/contaminants (e.g., heavy metals, pesticides, microbiological toxins).

## I. Stability Data for Oat Protein

Tate & Lyle's oat protein product PrOatein® meets the above analytical specifications. Stability testing of PrOatein® has been conducted at room temperature, 0°C, and 40°C for up to 18 months. After an 18-month storage period under a variety of storage conditions, PrOatein® was found to be stable in terms of protein content, dry matter, β-glucan content, pH, appearance, color, volumetric weight (density), and microbiological parameters. Tate & Lyle currently

recommends use "before 12 months after production." Stability test results can be found in Appendix D.

## 3.0 History of Use/Regulatory Approval of Cereal-Based Protein and Oat Protein

There is common knowledge of a long history of human consumption of oats. Oats contain the highest protein content of all the common grains (Katz, 2001). Tate & Lyle currently markets oat protein (PrOatein®) outside of the U.S. Additionally, similar oat-derived protein products are currently marketed in the U.S. (e.g., 55Oat Protein, Oat Tech, Inc.). Humans have consumed oats and the proteins from oats as well as other food sources providing protein such as meat, dairy, eggs, fruits, vegetables, grains, nuts, and seeds for centuries. Oats have been cultivated around the world for more than 2000 years. The U.S., Germany, Russia, Canada, France, Finland, Poland, and Australia are the largest producers of oats (FDA, 2013). Numerous food products containing oats are currently marketed in the U.S. and around the world. In addition, there has been a global demand for less expensive proteins with good nutritional and functional properties (Ma, 1983). Oat protein has become a desirable ingredient for addition to a variety of food products as a source of dietary protein due to its protein quality, and excellent amino acid profile as compared to soy protein (Cluskey et al., 1979).

Epidemiological studies and clinical trials have consistently revealed the cardiovascular benefits of oat consumption due to its hypocholesterolemic effects. In 1997, the FDA approved a health claim for the association between oat consumption and coronary heart disease (Katz, 2001; FDA, 1997).

Protein is found throughout the body, in muscle, bone, skin, hair, and virtually every body part or tissue. At least 10,000 different proteins are found in the body. Proteins are made up of amino acids that act as building blocks to make all types of protein. Some amino acids cannot be made by the body and therefore must be provided by the diet (i.e., essential amino acids). Around the world (but not in the U.S.), many people do not get enough protein in their diet leading to protein malnutrition, resulting in a condition known as kwashiorkor. While animal sources of protein tend to deliver all the amino acids the body requires, other plant protein sources also deliver most of the essential amino acids and have become an important source of added protein in processed food. Current plant and cereal grain sources of added protein used in food include peas, lentils, soy, canola, rice, chickpeas, beans, wheat, and potato.

FDA has established a daily reference value (DRV) for protein of 50 g/day for adults and children four or more years of age. Furthermore, Dietary Guidelines for Americans (HHS/USDA, 2005) recommend that adults eat half their grains as whole grains, which include oats and wheat. The Institute of Medicine (IOM, 2005) recommends that adults consume a minimum of 0.8 grams of protein per kilogram of body weight. IOM also set a wide range for acceptable protein intake, ranging from

10 - 35% of calories each day. In the U.S., the recommended daily allowance of protein is 46 grams/day for women over 19 years of age, and 56 grams/day for men over 19 years of age.

To date, FDA has reviewed extensive published information and data as part of GRAS notifications for animal and plant-based protein isolates and concentrates and subsequently issued "no questions letters" (e.g., GRN No. 26 (isolated wheat protein); GRN No. 37 (whey protein isolate and dairy product solids); GRN No. 168 (poultry protein); GRN No. 182 (hydrolyzed wheat gluten isolate; pea protein isolate); GRN No. 313 (beef protein); GRN No. 314 (pork protein); GRN 386 (canola protein isolate and hydrolyzed canola protein isolate); GRN No. 447 (potato protein isolates)).

## 4.0 Intended Use and Estimated Intake (EDI)

*Estimated intake*

The focus of this GRAS assessment is for an identical food use of oat-derived protein as previously recognized in the GRNs identified above for current grain-based protein sources such as soy, canola, pea, lentils, wheat, rice, and whey. Similarly, oat-derived protein will be used as a source of protein for enrichment of processed foods. As described in GRN No. 386 (see below) for canola protein isolate and hydrolyzed canola protein isolate, the typical uses of protein for enrichment of foods includes bakery products, snack foods, nutritional beverages such as high protein drinks and milkshakes, instant powdered nutritional beverages, vegetarian food products and meat analogues, dairy products, and meal replacements/nutritional bars.

**Application Usage Estimates**

| Food Category | Maximum Use Level in Canola Protein Products (%) as consumed | |
|---|---|---|
| | Isolexx™ | Vitalexx™ |
| Bakery products (*e.g.*, breads, rolls, doughnut, cookies, cakes, pies, batters, muffins, pasta, and cereal bars, etc.) | 3 | -- |
| Snack foods (*e.g.*, crackers, cookies, candy ingredients, breakfast/energy bars, snack chips, etc.) | 20 | -- |
| Beverages, soups, nutritional beverages (*e.g.*, protein fortified soft drinks, fruit juices, high protein drinks) | 5 | 5 |
| Dairy products (*e.g.*, cheese, frozen dairy dessert, whipped topping, yogurt, coffee whiteners, etc.) | 4 | -- |
| Dry instant milkshake mixes and protein drinks | 9 | -- |
| Instant powdered nutritional beverages | -- | 15 |
| Processed Meat products (where the addition of vegetable proteins are acceptable, such as unspecified products or those where they are included within the Standard of Identity) *(subject to USDA approval)* | 2 | -- |
| Vegetarian food products and meat analogues | 20 | -- |
| Meal replacement/nutritional bars | 30 | 25 |

The proposed use concentrations and variety of food uses combined with the large average daily consumption of the described foods resulted in the calculated daily intake of the protein additives being a substantial fraction of the RDA (46 grams/day for women over 19 years of age, and 56 grams/day for men over 19 years of age), and even exceeded it at the 90$^{th}$ percentile consumption. This was also the case for GRN No. 327 (cruciferin-rich canola/rapeseed protein isolate and napin-rich protein canola/rapeseed protein isolate). As Tate & Lyle's proposed oat protein is only intended to be an alternative source of protein for current uses in food, a similar estimate of intake would be expected if oat protein was the only source of protein used in processed foods. As other GRAS notifications have stated, we do not realistically expect that the actual consumption of foods containing oat protein would result in daily consumption greater than the DRV or RDA for protein. It is reasonable to expect that most of the population's intake of protein is, and will remain, in the form of unprocessed foods including meat, poultry, fish, and legumes. As the proposed oat protein product is only one of many protein sources for use in processed foods, only the inherent conservatism of intake calculations such as those described in the aforementioned GRNs suggest the possibility of exceeding the RDA at the 90$^{th}$ percentile (FDA, 2011; FDA, 2010).

In summary, the proposed uses of PrOatein® will not result in an increase in the overall consumption of protein, but simply provide an alternative source of well-characterized protein from oats for use in food. Therefore, cumulative intake analysis is not considered necessary.

*Self-limiting use*

The use of oat protein in protein-enriched foods is considered to be self-limiting for technological reasons such as product texture and/or flavor profile either of which could affect consumer acceptability.

# 5.0 Safety

## A. Introduction

Tate & Lyle currently markets oat protein (PrOatein®) outside of the U.S. However, oat protein products are currently marketed in the U.S. (e.g., 55Oat Protein, Oat Tech, Inc.). Humans have consumed oats and proteins from oats and other grains for centuries, along with proteins from many food sources such as meats, fruits, vegetables, nuts and seeds. Oats have been cultivated around the world for more than 2000 years. The U.S., Germany, Russia, Canada, France, Finland, Poland, and Australia are the largest producers of oats (FDA, 2012). Numerous food products containing oats are currently marketed in the U.S. and around the world. Healthy diets include high-quality proteins (de Pee and Bloem, 2009) and high-protein diets may help with weight loss (Martin et al., 2005). In their MyPlate campaign, the US Department of Agriculture (USDA) recommends that half of one's meal consist of

protein foods and grains (equal amounts), and the other half should contain fruits and vegetables, with an added serving of dairy (USDA, 2014).

According to the World Health Organization (WHO, 2002):

> *A source of protein is an essential element of a healthy diet, allowing both growth and maintenance of the 25,000 proteins encoded within the human genome, as well as other nitrogenous compounds, which together form the body's dynamic system of structural and functional elements that exchange nitrogen with the environment. The amount of protein that has to be consumed, as part of an otherwise nutritionally adequate diet, to achieve the desired structure and function is identified as the requirement.*

Oats are a popular cereal used for both human and animal foods due to the presence of high levels of protein and fatty acids. The protein content in oats is reported to be one of the highest among cereal grains (12-24%) and oats represent high quality protein. Oat proteins contain a nutritious amino acid composition, which is likely related to the high amount of lysine and higher proportion of globulins and albumins compared to proteins derived from other cereal grains. Oat proteins are 70-80% globulin. In oats, globulin (called avenalin) is the main storage protein. Prolamins (called avenin) are only a small fraction (Anderson, 2014; Nesterenko et al. 2013; Tsopmo et al., 2010; Wu et al., 1972). Over 40 years ago, Wu and co-workers (1972) stated:

> *The availability of high-protein oats, the favorable solubility properties of oat proteins, and their well-known nutritive value indicate a bright future for low-cost, high-protein, and highly nutritious food products being made from oat fractions.*

In oats, the majority of the metabolically active proteins, generally enzymes, are in the water-soluble albumin fraction. Enzymes present include maltase, α-amylase, proteases, lipases, lichenase, phenoxyacetic acid hydroxylase, tyrosinase, and phosphatase. Protease inhibitors, considered to be anti-nutritional, are also present. Oats are very nutritious; oat proteins exceed the requirements for all essential amino acids in children except threonine and lysine (Richman, 2012; Oats and Health, 2014).

The majority of safety-related information specifically pertaining to oat protein focuses on the potential for immune responses and intolerance in individuals with celiac disease. Celiac disease (CD) is an autoimmune condition with immunological, environmental and genetic components. In persons with CD, consumption of wheat gliadin/gluten and similar proteins elicits an immune response in the small intestine, causing inflammation and villous atrophy (Hoffenberg et al. 2000; Real et al., 2012; Thompson, 1997; Pulido et al., 2009).

## B. Safety Data

As would be expected for a food product widely consumed by humans for thousands of years, oats and oat proteins have not be subjected to traditional animal toxicology studies. The proteins in PrOatein® Oat Protein are the same as those found in oats, but in a more concentrated and isolated form. In addition, oats have been widely consumed by animals for centuries; horses as a major component of their diet and also cattle, swine, and dog feed/food, all without reported adverse effect. Several substantially similar protein isolates from other grain and plant sources have received GRAS designation, including wheat protein, canola protein and potato protein (FDA, 1999, 2011, and 2013, respectively). A chemically similar (i.e., amino acid profile) protein isolate from canola was recently tested for toxicity in a 90-day rat study and found to be without adverse effect (NOAEL of 20% in the diet, equivalent to 11.24 g/kg bw/day for males and 14.1g/kg bw/day for females). Given the information/data on the safety of oats and its common use in the diet of both humans and animals, conduct of toxicity studies on oat protein were considered unnecessary and not an ethical use of laboratory animals. A summary of the available safety information for oat protein and protein isolates considered substantially similar are presented below.

### Absorption, Distribution, Metabolism, and Excretion (ADME)

Protein and its breakdown products, peptides, amino acids and nitrogen, are required for maintenance of the human body (Bricker et al., 1945; WHO, 2002). Protein uptake can be confirmed by nitrogen absorption and retention (de Pee and Bloem, 2009). Dietary nitrogen is required to produce a sufficient flow of amino acids to maintain health (nitrogen balance; body weight; metabolic, physiological and psychological function) (WHO, 2002).

Oats can be a source of proteins with high nutritive quality, digestibility >90%, net protein utilization of 70%, and biological value around 75% (Oats and Health, 2014). Dietary oat proteins would therefore be expected to be almost completely digested and absorbed from the upper gastrointestinal (GI) tract by the time they reach the terminal ileum. Oat proteins would be broken down by gastric juices in the stomach and proteases in the small intestine and efficiently absorbed as small peptides or amino acids. Sherman and co-workers (1919) demonstrated that proteins present in oatmeal were very efficiently utilized in the maintenance metabolism of healthy adult volunteers. This indicates that oat proteins are effectively broken down into their constituent amino acids and small peptides that are typical of all food proteins. The known metabolism of oat proteins is a strong indicator of the safety of oat protein isolate.

### Human and Animal Studies of Oats, Oat Protein, and/or Other Protein Isolates

According to USDA (2014), commonly consumed proteins include meat, seafood, beans and peas, poultry, eggs, processed soy products, seeds and nuts. A variety of protein-containing foods are necessary for adequate intake of all essential amino

acids. In children at risk for malnutrition, de Pee and Bloem, (2009) recommend protein powder and protein extracts for children lacking adequate micronutrients and essential amino acids.

The antioxidant properties of many food protein concentrations and isolates (soy, milk, bean and chickpea) have been reported in the literature. Nutritional and functional properties of these food proteins can be enhanced using enzymatic hydrolysis. Following proteolytic hydrolysis of food proteins, various physiological activities have been found including radical scavenging, antihypertensive, immunomodulatory, antimicrobial, mineral binding and opioide activities (Tsopmo et al., 2010).

Graham et al. (1990) administered whole groat oat flour to 9 young children and infants as 22.5, 45, or 67% of total dietary energy (i.e., one half of 6.4%, all of 6.4%, or all of 9.6% protein energy). Controls consumed casein diets containing the same nitrogen and energy content. Absorptions of carbohydrate, fat and oat energy, as percentages of intake, decreased disproportionately as the oat flour intake increased. Apparent absorption of oat nitrogen measured approximately 75% of intake (casein, 87%). In children consuming 45% oats, fasting plasma free total essential amino acid levels were low and remained relatively constant after meals. Fasting molar proportions of individual essentials did not significantly vary 3 and 4 h after meals and were similar to those from milk protein consumption, which indicates that protein digestibility instead of an individual amino acid was first limiting to the retention of nitrogen. The authors concluded that oats are a satisfactory source of protein, fat and energy for infants and young children.

Bauer et al. (2013) discussed research indicating that older adults need more dietary protein than younger adults to support good health, promote recovery from illness, and maintain functionality. It is known that older adults need to make up for age-related changes in protein metabolism, such as high splanchnic extraction and declining anabolic responses to ingested protein. They also require more protein to offset inflammatory and catabolic conditions associated with chronic and acute diseases that occur commonly with aging. As a result, the European Union Geriatric Medicine Society (EUGMS), in cooperation with other scientific organizations, appointed an international study group to review dietary protein needs with aging (PROT-AGE Study Group). To help older people (>65 years) maintain and regain lean body mass and function, the PROT-AGE study group recommended average daily intake of at least 1.0 to 1.2 g protein per kilogram of body weight per day. Both endurance- and resistance-type exercises were recommended at individualized levels that are safe and tolerated, and higher protein intake (i.e., $\geq$ 1.2 g/kg body weight/day) was advised for those who were exercising and otherwise active. Most older adults who have acute or chronic diseases require even more dietary protein (i.e., 1.2-1.5 g/kg body weight/day). Older people with severe kidney disease but who are not on dialysis are an exception to the rule and those individuals may need to limit protein intake. Protein quality, timing of ingestion, and intake of other nutritional

supplements may also be relevant, but the authors indicated that the evidence is not yet sufficient to support specific recommendations

Regarding oats, oat consumption has various health benefits, such as a decreased risk of coronary heart disease and lowering of low-density lipoprotein (LDL) cholesterol (FDA, 1997; Davy et al., 2002). In their meta-analysis of the literature and of unpublished trials on the cholesterol lowering effects of oat products, Ripsin et al. (1992) indicated that the addition of oat products to a diet yields a modest reduction in blood cholesterol level. For the 10 studies meeting the inclusion criteria, a summary effect size for change in blood total cholesterol level of -5.9 mg/dL (95% CI, -8.4 to -3.3 mg/dL) was calculated. The summary effect size for studies using wheat control groups was -4.4 mg/dL (95% CI, -8.3 to -0.38 mg/dL). The greatest reductions in blood cholesterol were seen in trials where participants had initially higher blood cholesterol levels (≥229 mg/dL). The authors concluded that their analysis provides strong support for the hypothesis that approx. 3 g/day soluble fiber from oat products can lower the total cholesterol level by 5-6 mg/dL. β-glucan concentrations were not specified.

Zhou and co-workers (2015) fed whole grain oat (WGO) flour or low bran oat (LBO) flour to 5-week-old male C57BL/6J mice for 8 weeks. Animals in the WHO group exhibited a 14.6% decrease in weight gain during week 7 (P= 0.04) and decreases in plasma total (9.9%) and non-HDL (11%) cholesterol. WGO improved insulin sensitivity, as demonstrated by significantly lower plasma insulin, C-peptide, and homeostasis model assessment-estimated insulin resistance. These effects were associated with alterations in cecal microbiota composition. Therefore, relative to LBO, WGO improved the plasma cholesterol profile and insulin sensitivity in mice. The authors concluded that increasing WGO consumption may help improve dyslipidemia and insulin sensitivity in chronic diseases.

Avenanthramides are polyphenols found in oats alone and may be involved in antiatherogenesis and anti-inflammation. Wang et al. (2015) studied the metabolism of avenanthramide-C (2c), an antioxidant, in mice and by the human microbiota, and evaluated the bioactivity of its major metabolites to identify new exposure markers to precisely reflect oat consumption. In urine from female CF-1 mice treated intragastrically with 2c (200 mg/kg), eight 2c metabolites were identified. In cultures of 2c with fecal slurries from 6 human donors, four 2c metabolites were identified. Avenanthramide-C and its major metabolite M4 were bioactive against HCT-116 human colon cancer cells, inhibiting cell growth and inducing apoptosis. The authors concluded that this is the first study to show that 2c from oats can be substantially metabolized by mice and the human microbiota to yield bioactive metabolites.

Mejia et al. (2009) conducted a study with the test article Puratein®, a cruciferin-rich canola protein (minimum 90% protein; GRN No. 327) with an amino acid profile that was very similar to that of PrOatein® found in Figure 2. Rats were fed ad libitum at levels of 5%, 10% and 20% for 90-days. Four groups of Crl:CD Sprague Dawley rats (20/sex/group) were used in the study, following FDA Red Book Guidelines. The

animals were fed an AIN-93 diet, with the lower doses adjusted with casein to the required level of at least 18% protein in rodent diets. There were no treatment related effects in the animals fed Puratein® at any dose. These included survival, clinical, and functional observations. Food consumption was equivalent at all doses and body weight gains were the same for all animals of the same sex at all doses. While there were sporadic changes in neutrophil counts in 10% and 20% -treated females on study day 45, a similar trend was not seen for males, and the neutrophil counts for the females returned to normal on study day 91. There were no treatment related changes in serum chemistry or urinalysis. There were some non-dose related differences in some serum chemistry parameters (potassium, sorbitol dehydrogenase, alkaline phosphatase). The differences were very small and were not considered toxicologically significant. There were no treatment-related changes. The NOAEL for the dietary administration of Puratein® was the highest dose tested, 20% in the diet, equivalent to 11.24 g/kg bw/day for males and 14.1g/kg bw/day for females.

A GRAS notification for canola protein (FDA, 2011) stated that there is no scientific justification for performing mutagenicity tests on purified proteins. Pariza and Johnson (2001) reviewed the history of genotoxic testing of microbial enzymes used in food processing, and concluded no clastogen or mycotoxin has ever been identified that would not have been detected by limited animal feeding studies and properly conducted analytical chemistry analyses. Further, a series of clastogenicity and mutagenicity studies on canola proteins, as reported in GRAS Notification No. 327 showed negative results for canola proteins (FDA, 2011). Similar negative genotoxicity results would be expected from oat protein testing.

In summary, studies of oats, oat protein, and other protein isolate sources in humans and/or animals have demonstrated its beneficial effects as well as safety. Studies with other protein sources with similar amino acid profiles to oat protein have also demonstrated a lack of toxicity at high levels of consumption. Furthermore, given that the metabolism of oat protein to its constituent amino acids, peptides, and nitrogen is well understood and other protein isolate products derived from wheat, canola, and potatoes have a GRAS designation, the proposed oat protein product can also be considered safe as proposed for human consumption

**Reported Safety Concerns**

Extremely high protein consumption may be toxic. In persons who consumed diets consisting of 45% protein from rabbit meat (a very low fat diet), nausea and diarrhea occurred in 3 days, and death within several weeks. Preterm infants fed high-protein formula experienced lethargy, fever, poor feeding and increased incidence of strabismus and low IQ scores at 3- and 6-year evaluations. While it has been recommended that adults not consume more than two-fold the reference dietary amount of 1.5 g protein/kg, physically active individuals on normal diets easily exceed this amount, and persons involved in body-building consume much higher levels of protein (WHO, 2002). WHO (2002) recommends protein consumption rates for both sexes combined based on body weight. For example, the safe protein level

for a 40-kg adult is 33 g/kg/day; that for an 80-kg adult is 66 g/kg/day. In terms of nitrogen, WHO (2002) reports the median adult protein requirement as 105 mg nitrogen/kg/day, with the 97.5 percentile value as 132 mg nitrogen/kg/day. PrOatein® is not intended for use in infant formula and its proposed food use result in consumption levels well below the safe protein consumption levels cited above.

*Renal Function*

Dietary protein can influence renal function. Increased protein intakes yield increased excretion of creatinine and urea, due to increased glomerular filtration rate (GFR) resulting from increased renal blood flow. Concern has historically been expressed that excess protein intake can promote chronic kidney disease via hyperfiltration and increased glomerular pressure (Martin et al., 2005; WHO, 2002). After a critical review of the literature, Martin et al. (2005) concluded that while protein restriction may be recommended for treatment of existing kidney disease, no significant evidence exists for a detrimental effect of high protein intakes on renal function in healthy persons after hundreds of years of high protein Western diets. In fact, several studies suggest that hyperfiltration, the suggested mechanism for kidney damage, is a normal adaptive response to increased nitrogen load and higher demands for renal clearance. The authors considered "high protein diet" as daily intake ≥1.5 g/kg-day, which is within the range of current Dietary Reference Intakes for protein and nearly twice the current Recommended Dietary Allowance. In persons with pre-existing kidney disease, increased dietary intake of animal protein has been found to accelerate the disease, but the association was not found in persons with healthy kidney function. In patients with compromised renal function, a high protein diet which results in a renal solute load in exceeding the kidneys' excretory abilities can contribute to progressive renal failure (Martin et al., 2005). Again, the proposed is not intended for use in infant formula and its proposed food use of PrOatein® results in consumption levels below those associated renal function concerns.

*Calcium Balance*

There is the potential for excess protein consumption to adversely affect the body's calcium balance and calcium in bone. High-protein diets can lead to increased urinary calcium excretion; doubling protein intake can amount to a 50% increase in urinary calcium. Further, increased resorption of bone is associated with increased protein intake. However, it appears that as part of a well-balanced diet, dietary protein is likely to be beneficial for bone, even possibly at dietary levels exceeding the recommended intakes (WHO, 2002).

*Kidney Stones*

An additional potential consequence of a high-protein diet is an increased incidence of kidney stones. Kidney stones are fairly common, and have been estimated to affect 12% of the US population. Urine is high in calcium and oxalate, and studies have shown that an increase in animal protein intake led to increased urinary calcium and

oxalate, which was estimated to increase the likelihood of stone formation. However, conclusions cannot be drawn from the various studies, since dietary impacts occurred only in studies with a wide range of protein intakes (e.g., 80-185 g/day). Further, it was unclear whether there is a difference between plant and animal proteins. Therefore, it is recommended that to decrease the risk of kidney stones in those who are at risk, the diet should provide at least the safe level of protein (0.83 g/kg-day), ideally from vegetable sources, but not large amounts (<1.4 g/kg-day), (WHO, 2002).

*Allergy*

Allergy manifestation resulting from consumption of oats and oat products has been debated, and it has been alleged that oats may cause adverse effects in individuals with CD. Oats and protein are not listed among FDA's list of the 8 major food allergens (FDA, 2010).

However, children with atopic dermatitis and farmers with allergies to grain dust may experience allergic reactions to oat proteins. These proteins can act as skin and respiratory allergens (Boussault et al., 2007; FDA, 2012).

*Celiac Disease*

Regarding oats, some studies of patients with celiac disease (CD) indicate more frequent GI symptoms while consuming an oat-containing gluten-free diet (GFD) than consumption of a traditional GFD. Such symptoms are generally mild, and the appearance of flatulence and abdominal distension has previously been attributed to the increased intake of fiber from oat products (Holm et al., 2006; Pulido, 2009).

CD is an autoimmune condition with immunological, environmental and genetic components. In persons with CD, consumption of wheat gliadin/gluten and similar proteins elicits an immune response in the small intestine, causing inflammation and villous atrophy. It has been estimated that CD affects 1 in 250 Americans, many of whom have asymptomatic or "silent" CD, which may be 5-7 fold more common than symptomatic CD (Hoffenberg et al. 2000; Real et al., 2012; Thompson, 1997; Pulido et al., 2009).

Oats may increase the palatability of a gluten-free diet (GFD) and can be a valuable source of fiber in a diet that is typically fiber deficient (Lundin et al. 2003). Further, a GFD is very restrictive. If CD patients can consume oats, the restrictive nature of the diet would be reduced, which could then lead to an increase in the quality of life (Richman, 2012). In a systematic review of the clinical literature regarding the presence of oats in the diets of individuals with CD, Pulido et al. (2009) stated that incorporation of oats into a GFD provides increased palatability, high vitamin B and fiber content, and beneficial impacts on cardiovascular health.

Studies reported in the literature present contradictory information regarding if oats can elicit abnormal immunological responses in persons with CD. Koskinen et al. (2009) evaluated the toxicity of oats in 23 children (median age 13 years, range 7–18 years, 7 female) with CD in remission during a 2-year follow-up by measuring jejunal transglutaminase 2 (TG2)-targeted IgA-class autoantibody deposits, which is likely a more sensitive disease marker than conventional histology or serum antibodies. Participants consumed oats and were randomized to undergo a gluten challenge allowing the consumption of wheat, rye, and barley in addition to oats. When histological relapse in the small intestine occurred after gluten challenge, patients continued to consume oats but not the other grains. At the beginning of the study, serum TG2 antibodies were negative in all participants, but 7 children had minor mucosal deposits. In the group that underwent the gluten challenge, the deposits clearly increased then decreased again when other grains were excluded and oat consumption continued; the same pattern occurred with the serum autoantibodies. In the group consuming oats, no significant change in the intensity of the deposits occurred within 2 years. The authors concluded that in children with CD, oat consumption does not induce TG2 autoantibody production at the mucosal level. These results showed that oats were tolerated by most CD patients, and were neither immunogenic nor toxic to the small-bowel mucosa.

Kemppainen and co-workers (2007) conducted a study demonstrating the long-term safety of inclusion of oats in a diet for patients with CD. In the study, the authors analyzed local cellular immunological responses after 5 years of oats consumption by adults with CD. Forty-two coeliac patients took part in an earlier oat intervention study for 6-12 months. Over a 5-year period, 20 celiac patients on a strict, conventional, GFD without oats served as the control; 12 celiac patients consumed oats. There were no differences in the densities of intraepithelial abIEL, CD3, and gdIEL T cells between the oat vs. control groups. The authors concluded that chronic oat consumption as part of a GFD in persons with CD does not initiate a local immunological response in the mucosa of the small intestine.

Sjoberg et al. (2014) investigated whether oat consumption can influence the immune status of the intestinal mucosa in children with CD. In children who had been on a GFD for >11 months, paired small intestinal biopsies were collected. Children participated in the randomized, double-blind intervention study by consuming either a standard GFD (5 boys, 8 girls, 4.2±3.5 years) (control) or a GFD containing non-contaminated oats (7 boys, 8 girls, 5.8±4.7 years). The authors measured expression levels of mRNAs for 22 immune effector molecules and tight junction proteins via quantitative reverse transcriptase polymerase chain reaction. In the group consuming oats, the number of mRNAs that remained elevated was significantly higher. The most significant differences were seen for KLRC3/NKG2E and claudin-4. However, only certain aspects of mucosal immunity seem to be affected; markers of down-regulatory and cytotoxic activities were not impacted. The authors concluded that a notable fraction of children with CD seem to not tolerate oats. In these children, oat consumption alters the immune status of the intestinal mucosa, and the mRNA profile suggests a stressed epithelium with affected tight junctions and the presence of

activated cytotoxic lymphocytes and regulatory T cells. It appears that even avenin can cause an immune response in the intestinal mucosa in some CD patients, either on its own or by cross-reactivity. Pediatric CD patients with sensitivity to oats can be identified by assessing changes in mRNA levels for claudin-4 and KLC3/NKG2E from onset to after 1 year consuming oats as part of a GFD.

Real et al. (2012) conducted a study to evaluate the safety of prolamins from oat varieties with low, medium, and high reaction for CD patients. The avenin genes of these oat varieties were cloned and sequenced, and their expression measured throughout the grain development. The avenin sequences were classified into three different groups, which possess homology with the S-rich prolamins of Triticeae (barley, wheat and rye). Avenin proteins had a lower proline content than wheat gliadin, which may contribute to the low toxicity of oat avenins. A direct relationship was observed between the immunogenicity of the different oat types and the presence of the specific peptides with the potential for higher/lower immunotoxicity. The authors concluded that range of variation of potential immunotoxicity of oat cultivars varies widely, and this variation could result from differences in the level of immunogenicity in their sequences.

In an *in vitro* study, Maglio and coworkers (2011) investigated the immunological and biological properties of two oat varieties, *Avena potenza* and *Avena genziana*, to determine their safety for persons with CD. In contrast to peptic–tryptic digests from gliadin, the oat peptic–tryptic digests did not induce a significant decrease in transepithelial electrical resistance or an increase in extracellular signal-regulated kinase phosphorylation in CaCo-2 cells. In duodenal biopsies from 22 persons with CD, unlike the response to gliadin, oat digests did not significantly increase interleukin 15 expression, lamina propria CD25+ cells, nor crypt enterocyte proliferation. However, in 3/8 CD intestinal T cell lines, *Avena genziana* induced IFN-g production, and *Avena potenza* increased the density of intraepithelial T-cells. The authors concluded that the data showed that *Avena potenza* and *Avena genziana* do not display activities related to CD pathogenesis. Some of the observed T-cell reactivity may be below the threshold of clinical relevance.

In another *in vitro* study, Silano et al. (2014) evaluated the ability of three different oat varieties to activate gliadin-induced transglutaminase-2 (TG2)-dependent events in various *in vitro* CD models. This effect was also compared with the electrophoresis pattern of peptic–tryptic digests of the proteins of the oat varieties. The Nave oat cultivar triggered such events, but Irina and Potenza varieties did not. Further, results showed that a cultivar's ability to initiate these events was directly related to the electrophoretic pattern of the proteins and their reactivity to anti-gliadin antibodies. The authors concluded that before beginning a clinical trial, an oat variety's safety to CD patients could be screened by such *in vitro* biochemical and biological assays.

Previous studies have demonstrated that monoclonal antibodies (moAbs) against the primary immunotoxic 33-mer peptide (A1 and G12) react strongly against wheat, rye

and barley, but less against oats. Comino et al. (2011) tested whether this reactivity may be related to the potential toxicity of oats in CD patients. The authors determined the immunogenicity of three oat varieties via interferon g production, 33-mer concentration and T cell proliferation using Western blot and ELISA. The three groups of oat cultivars reacted differently against moAb G12: substantial affinity, slight reactivity and no detectable affinity. Immunogenicity of the three oat types was assessed using isolated peripheral blood mononuclear T cells from patients with CD, by measuring interferon g release and cell proliferation. Potential immunotoxicity of the different prolamins was directly proportional to their reactivity with G12. Since immunogenicity differed between the oat cultivars, this may explain why some oats trigger an immunological response in CD patients. Further, these results indicate that the specific antibody is a reliable instrument for detecting oat varieties that are potentially safe for patients with CD (Comino et al. 2011).

Using a solid-phase radioimmunoassay, Troncone and co-workers (1987) examined sera from 6 children (median age 1.9 years, range 1-2.5 years; gender not reported) with active CD. The sera were examined for IgG antibodies against different cereal proteins. Similarly, elevated titers against gliadin from six age-matched controls were also examined. In coeliac sera, rice prolamins gave lower titers but high titers were measured when tested against oats, barley, and maize prolamins, as well as wheat albumins, glutenin and globulins. The authors concluded that these results indicated a dissociation between toxicity in CD patients and immunogenic properties of cereal proteins.

Using Western blotting, Freedman et al. (1988) created two monoclonal antibodies raised against wheat gliadin, and determined antibody binding to different cereal protein fractions. There results showed significant epitope sharing between rye and barley prolamins as well as gliadin subfractions, but less binding of the antibodies to oat avenins. The authors noted that the binding pattern closely corresponded to the toxicity of these proteins to persons with CD.

Various *in vivo* and *in vitro* studies support different conclusions with regards to the immune response elicited by oats in patients with CD. In the studies in which a response was observed, the data indicate that certain oat varieties may be immunogenic, but others are not. As further noted below, food product ingredient lists would state the presence of an oat-protein ingredient, and individuals who wish to avoid oats consumption for any reason would be able to identify the presence of an oat-derived ingredient.

*Celiac Disease and Gluten Free Diets*

Globulins are the major storage proteins in oats. Conversely, prolamins are the main storage protein in barley, wheat and rye. Common cereal prolamins include gluten (primarily in wheat) and zein (in maize). In wheat, barley and rye, gluten accounts for between 30-60% of the total protein. The small amount of prolamins present in oats are primarily avenins, which may make oats an option for those with gluten

allergies (Oats and Health, 2014). Avenin accounts for 10-15% of the total protein in oats. The amino acid sequences believed to cause toxic responses in persons with CD are much less frequent in avenin than in gluten (Hoffenberg et al. 2000; Holm et al., 2006).

Historically, use of oats in GFDs has not been allowed. Evidence from more recent reports indicates that oats are safe for consumption by most individuals with celiac disease (Rashid et al., 2007). Health Canada (2007) critically reviewed the scientific literature and concluded that the majority of people with celiac disease can tolerate moderate amounts of pure oats that are uncontaminated with other cereal grains such as wheat, barley and rye. It is recognized that commercially available oats are variably contaminated with gluten-containing grains that can occur on the farms, during the growing cycle or during storage, cleaning, transportation or processing.

Historically, oat consumption by celiac disease patients was not widely recommended in the U.S. due to concerns of potential contamination of commercial oats (Kupper, 2005; American Celiac Society, 2014). According to the National Foundation for Celiac Awareness (NFCA, 2014), although oats do not contain gluten, a small percentage of persons with celiac disease react to pure, uncontaminated oats. Further, most mills that process oats also process grains that contain gluten, making cross contamination likely. However, up to 50 g /day of dry, gluten-free oats is now considered safe (NFCA, 2014).

Dickey and co-workers (2007) note that not every person with CD can tolerate pure oats. Some participants withdrew from oat challenge studies due to adverse gut symptoms. These symptoms were usually not associated with histological relapse, were temporary, and were not significantly more frequent than in groups on a GFD who were not consuming oats (Dickey, 2007).

The majority of studies suggest that oats can be tolerated by most CD patients. Hoffenberg et al. (2000) performed a study to assess whether oat consumption is safe in children who have been recently diagnosed with CD and are beginning a GFD. Ten children (6.8±4.0 years of age; 5 males, 5 females) completed the 6.6-month, self-controlled, open-label trial where they consumed commercial oat breakfast cereal product (24 g/day, 1.2 ±0.9 g/kg-day). At study completion, there was a significant decrease in the number of symptoms, small bowel biopsy score, anti-tissue transglutaminase IgA antibody titer and intra-epithelial lymphocyte count. The authors concluded that consumption of the oat cereal product for 6 months was safe for children with CD who were starting a GFD. However, studies were recommended to determine the long-term safety of oat cereal consumption for pediatric CD patients.

In a 2-year clinical trial, Holm and co-workers (2006) evaluated 32 children with CD to study the long-term safety of oats in the treatment of children with CD. Nine children recently diagnosed with CD consumed an oat-containing GFD; 23 children in remission were challenged with either oats or gluten. In the gluten challenge

group, when small bowel histological relapse was evident, children were switched to a GFD including oats. After cessation of the trial, participants were allowed to freely consume oats; follow-up was up to 7 years. In the children who were in remission and consumed oats, no adverse effects on celiac serology or intestinal histology occurred during trial. In the gluten challenge group, however, relapses occurred after 3–12 months. During consumption of the oat-containing GFD, complete recovery occurred in all newly detected and relapsed patients. At the conclusion of the trial, all children remained in remission and 86% of the participants preferred to consume oats. The authors concluded that in most pediatric CD patients, long-term oat consumption did not result in immune activation or small bowel mucosal deterioration, and consumption was well-tolerated.

Sey et al. (2011) conducted a study whereby 15 adults (57±9 years, 2 males) with CD of ≥1 year duration were challenged with pure oats (350 g/wk) for 12 weeks. Duodenal histology scores were not significantly altered during oat challenge, and tissue transglutaminase remained negative in all participants. During oat consumption, no significant changes in symptom scores, albumin, ferritin, hemoglobin or weight occurred. There were no significant changes in mean pain, flatulence, diarrhea or abdominal distension scores. There was a single relapse, which was in a person who was noncompliant with a GFD. The authors concluded that this study supports the safety for CD patients of uncontaminated, pure oats manufactured under Canadian Celiac Association guidelines.

In CD patients, a rash, dermatitis herpetiformis, can occur when gluten is consumed. Reunala and co-workers (1998) conducted a study in 11 adults with CD to determine whether the participants could also tolerate oats. The volunteers included 5 men and 6 women, age 51 (range 30–67 years). Participants had dermatitis herpetiformis in remission, were on a GFD, and consumed oats at 50 g/day for 6 months. A separate control group of 11 volunteers with dermatitis herpetiformis in remission consumed a conventional GFD. Eight persons participating in the challenge with oats developed no symptoms, 2 experienced a transient rash, and 1 withdrew due to a mild but more persistent rash. A transient rash occurred in 3 of the controls. Densities of intraepithelial CD3 and $\alpha/\beta$ and $\gamma/\delta$ T cell receptor positive lymphocytes, crypt epithelial cell DR expression, and the villous architecture of small bowel remained unaltered; these changes are typically linked with the skin rash. IgA endomysial antibodies remained negative in all patients. The authors concluded that as oat toxicity on the gluten sensitive small bowel mucosa did not occur, and increased rashes were not observed in participants, dermatitis herpetiformis was not activated by eating oats.

Lundin et al. (2003) challenged 19 adults with CD who were on a GFD with oats (50 g/day) for 12 weeks. Before and after the oat challenge, gastroduodenoscopy and serological tests were performed. While oats were well tolerated by most participants, several experienced initial bloating and abdominal discomfort. One patient developed a rash and partial villous atrophy during the first challenge. The participant improved when oats were removed from the diet, but experienced

dramatic dermatitis and subtotal villous atrophy during a second oats challenge. After the challenge, 5 patients showed positive levels of interferon c mRNA. The authors concluded that, due to the development of villous atrophy and dermatitis in one participant, concerns remain regarding the safety of oats for persons with CD.

In her review of studies evaluating the safety of oats in individuals with CD, Richman (2012) states that earlier studies are difficult to evaluate, as they were conducted using different methodologies and it is unknown whether oat samples used in the studies were contaminated with gluten from other grains. Many studies do not specify the strain of oat used. Recent research suggests that perhaps only certain oats strains cause a toxic response in CD patients. While proteins in oats are similar to those in barley, wheat and rye, oat prolamins (avenin) have substantially lower levels of proline, one of the triggers for intestinal damage in persons with CD. The author concluded that research suggests that the risk from consuming oats may be less harmful than first thought, but it may vary according to the oat strain. Handling this issue in clinical practice remains controversial.

Pulido et al. (2009) similarly reviewed the literature regarding introducing dietary oats to persons with CD. The studies at the time had limited numbers of volunteers in studies, lacked sufficient data on long-term consumption, and insufficient reporting regarding reasons for withdrawals from the studies.

Concerns remain about potential contamination of commercially available oat products by rye, wheat and barley. While pure oats have been confirmed as having undetectable levels of barley, wheat and rye prolamins, many commercial oat products had unacceptable levels of contamination from other grains. In the UK, 41-59% of oat foods exceeded the limit of 200 ppm, and 12-26% were in the 20 - 200 ppm range (Dickey, 2007). Analysis of oats from a Canadian oat supply showed that approximately 88% of the 133 oat samples tested were contaminated with other grains >20 mg/kg, and there were no differences noted between the oat types (Koemer et al., 2011).

In summary, the majority of data indicate that oat consumption is safe for persons with CD as part of a GFD. However, some studies indicate that some individuals may experience adverse effects, and these may be oat strain-specific.

## C. Safety Data Summary

There is common knowledge of a long history of human consumption of oats. Oats have been cultivated around the world for more than 2000 years. Humans have consumed oats and proteins from oats and other grains for centuries, along with proteins from many food sources such as meats, fruits, vegetables, nuts and seeds. The U.S., Germany, Russia, Canada, France, Finland, Poland, and Australia are the largest producers of oats (FDA, 2012). Numerous food products containing oats are currently marketed in the U.S. and around the world.

Oat consumption has various health benefits, such as a decreased risk of coronary heart disease and lowering of cholesterol (FDA, 1997; Davy et al., 2002; Ripsin et al. 1992). Protein is necessary for a healthy diet; the Centers for Disease Control and Prevention (CDC, 2014) recommends that adult women and men consume 46 and 56 g protein per day, respectively. Further, several protein isolates have received GRAS designation, including wheat protein, canola protein and potato protein (FDA, 1999, 2011 and 2013, respectively).

WHO (2002) reports the digestibility of protein in oatmeal as 86% and that in cereal oats as 72%. Therefore, dietary oat proteins are expected to be almost completely digested and absorbed from the upper gastrointestinal (GI) tract by the time they reach the terminal ileum. Oat proteins would be broken down by gastric juices in the stomach and proteases in the small intestine and efficiently absorbed as small peptides or amino acids. Sherman and co-workers (1919) demonstrated that proteins present in oatmeal were very efficiently utilized in the maintenance metabolism of healthy adult volunteers. This indicated that oat proteins were effectively broken down into their constituent amino acids and small peptides that were typical of all food proteins. Therefore, the known metabolism of oat proteins is a strong indicator of the safety of oat protein isolate.

Oat protein isolates have been shown to have antioxidant activity. Following proteolytic hydrolysis of food proteins, various physiological activities have been found including radical scavenging, antihypertensive, immunomodulatory, antimicrobial, mineral binding and opioide activities (Tsopmo et al., 2010). Oat consumption decreases the risk of coronary heart disease and lowers LDL cholesterol (FDA, 1997; Davy et al., 2002; WHO, 2002). Oats are considered a satisfactory source of protein, fat and energy for infants and young children (Graham et al., 1990). Dietary protein has been shown to decrease blood pressure and may decrease the risk of cardiovascular disease (WHO, 2002).

Studies of oats, oat protein, and other protein isolate sources in humans and/or animals have demonstrated its beneficial effects as well as safety. Safety studies of other protein sources (e.g., canola protein isolates) with similar amino acid profiles to oat protein have also demonstrated a lack of toxicity at high levels of consumption.

Some studies of patients with celiac disease (CD) indicate more frequent GI symptoms while consuming an oat-containing gluten-free diet (GFD) than consumption of a traditional GFD. Such symptoms are generally mild, and the appearance of flatulence and abdominal distension has previously been attributed to the increased intake of fiber from oat products (Holm et al., 2006; Pulido, 2009). In women with breast cancer, high dietary protein intakes improved survival rates (WHO, 2002).

Extremely high protein consumption may be toxic. While it has been recommended that adults not consume more than two-fold the reference dietary amount of 1.5 g protein/kg, physically active individuals on normal diets easily exceed this amount,

and persons involved in body-building consume much higher levels of protein (WHO, 2002). Dietary protein can influence kidney function, and high protein diets may be linked with increased incidence of kidney stones in susceptible individuals (Martin et al., 2005; WHO, 2002).

Various *in vivo* and *in vitro* studies show different results relative to whether oats can elicit an immune response in patients with CD. In studies which showed a response, the data indicated that certain oat varieties may be immunogenic, but others are not.

Children with atopic dermatitis and farmers with allergies to grain dust may experience allergic reactions to oat proteins. These proteins can act as skin and respiratory allergens (Boussault et al., 2007; FDA, 2012).

There are conflicting data indicating whether CD patients can tolerate oats. Allergy manifestation resulting from consumption of oats and oat products has been the subject of debate. It has been alleged that oats may cause adverse effects in individuals with celiac disease. As a result, use of oats in a GFD was not allowed. However, recent evidence indicates that oats are safe for consumption by most individuals with celiac disease (Rashid et al., 2007). Health Canada (2007) critically reviewed the scientific literature and concluded that the majority of people with celiac disease can tolerate moderate amounts of pure oats that are uncontaminated with other cereal grains such as wheat, barley and rye. In fact, pure oats may be beneficial to persons with celiac disease, as its palatability may increase patients' compliance with a GFD (Health Canada, 2007).

It should be emphatically stated that the recommended ingredient labeling for PrOatein® is "oat protein." Thus, food product ingredient lists would state the presence of an oat ingredient and individuals who wish to avoid oats consumption for any reason would be able to identify the presence of an oat-derived ingredient.

# 6.0 Basis for the GRAS Determination

## A. Introduction

The regulatory framework for determining whether a substance can be considered generally recognized as safe (GRAS) in accordance with section 201(s) (21 U.S.C. § 321(s)) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 301 et. Seq.) ("the Act"), is set forth at 21 CFR 170.30, which states:

> General recognition of safety may be based only on the view of experts qualified by scientific training and experience to evaluate the safety of substances directly or indirectly added to food. The basis of such views may be either (1) scientific procedures or (2) in the case of a substance used in food prior to January 1, 1958, through experience based on common use in food. General recognition of safety requires common knowledge about the substance throughout the scientific community knowledgeable about the safety of substances directly or indirectly added to food.
>
> General recognition of safety based upon scientific procedures shall require the same quantity and quality of scientific evidence as is required to obtain approval of a food additive regulation for the ingredient. General recognition of safety through scientific procedures shall ordinarily be based upon published studies, which may be corroborated by unpublished studies and other data and information.

These criteria are applied in the analysis below to determine whether the use of an oat-derived protein for use in food for human consumption is GRAS based upon scientific procedures. All data used in this GRAS determination are publicly available and generally known, and therefore meet the "general recognition" standard under the FD&C Act.

## B. Safety Determination

The subject of this GRAS determination is the use of oat-derived protein as an alternative source of dietary protein for addition to processed foods. There is a long history of the safe use of oats and products derived from oats such as oat β-glucan and oat protein concentrates. Furthermore, other natural sources of protein concentrates, such as canola, potato, and wheat, have been safely consumed for years. Tate & Lyle currently markets oat protein (PrOatein®) outside of the U.S. However, oat protein products are currently marketed in the U.S. (e.g., 55Oat Protein, Oat Tech, Inc.). While there is a noted lack of published safety studies on oat protein concentrates, the safety section describes human safety studies of oats and oat protein as well as human and animal studies of other GRAS-notified protein sources currently added to processed foods.

The focus of this GRAS determination is a comprehensive assessment of the safety of an oat-derived protein for an identical use to that of other current grain-based protein sources such as soy, canola, pea, lentils, wheat, rice, and whey. Similarly, the nutritionally use is as a source of protein for enrichment of processed foods. The IOM recommends that adults consume a minimum of 0.8 grams of protein per kilogram of body weight. IOM also set a wide range for acceptable protein intake, ranging from 10 - 35% of calories each day. In the U.S., the recommended daily allowance of protein is 46 grams/day for women over 19 years of age, and 56 grams/day for men over 19 years of age.

As described in GRN No. 386 for canola protein isolate and hydrolyzed canola protein isolate, the typical uses of protein for enrichment of foods includes in bakery products, snack foods, nutritional beverages such as high protein drinks and milkshakes, instant powdered nutritional beverages, vegetarian food products and meat analogues, dairy products, and meal replacements/nutritional bars. The proposed use concentrations and variety of food uses combined with the large average daily consumption of the described foods resulted in the calculated daily intake of the protein additives being a substantial fraction of the RDA (46 grams/day for women over 19 years of age, and 56 grams/day for men over 19 years of age), and even exceeded it at the 90$^{th}$ percentile consumption. This was also the case for GRN No. 327 (cruciferin-rich canola/rapeseed protein isolate and napin-rich protein canola/rapeseed protein isolate). As Tate & Lyle's proposed oat protein is only intended to be an alternative source of protein for current uses in food, a similar estimate of intake would be expected if oat protein was the only source of protein used in processed foods. As GRAS notifications for other protein sources and isolates have previously noted, we do not realistically expect that the actual consumption of foods containing oat protein would result in daily protein consumption being any greater than the DRV or RDA for protein. It is reasonable to expect that most of the population's intake of protein is, and will remain, in the form of unprocessed foods including meat, poultry, fish, and legumes. As the proposed oat protein product is only one of many protein sources for use in processed foods, only the inherent conservatism of intake calculations such as those described in the aforementioned GRNs suggest the possibility of exceeding the RDA at the 90$^{th}$ percentile (FDA, 2011; FDA, 2010).

In summary, the proposed uses of PrOatein® will not result in an increase in the overall consumption of protein, but simply provide an alternative source of well-characterized protein from oats for use in food.

Oat consumption has various health benefits, such as a decreased risk of coronary heart disease and lowering of cholesterol and protein is necessary for a healthy diet. While there exists a lack of published preclinical safety studies on oat protein, products containing oats and other sources of grain-based protein concentrates have been employed in numerous clinical trials. Other than mild, transient gastrointestinal (GI) effects such as flatulence and abdominal discomfort, no significant adverse effects have been reported.

Some studies of patients with celiac disease indicate more frequent GI symptoms while consuming an oat-containing gluten-free diet (GFD) than during consumption of a traditional GFD. Such reported symptoms were generally mild, and the appearance of flatulence and abdominal distension has previously been attributed to the increased intake of fiber from oat products. The majority of data indicate that oat consumption is safe for persons with CD as part of a GFD. However, some studies indicate that a few individuals may experience adverse effects, and these may be oat strain-specific. It should be noted that the recommended ingredient labeling for PrOatein is "oat protein." Thus, food product ingredient lists containing PrOatein would state the presence of an oat ingredient as "oat protein" and individuals who wish to avoid oats consumption for any reason would be able to identify the presence of an oat-derived ingredient.

## C. General Recognition of the Safety of Oat Protein

The intended use of oat protein has been determined to be safe through scientific procedures as set forth in 21 CFR§170.3(b), thus satisfying the so-called "technical" element of the GRAS determination and is based on the following:

- PrOatein® Oat Protein is manufactured consistent with current Good Manufacturing Practice (cGMP) for food (21 CFR Part 110). The raw materials used in the manufacturing process are food grade and/or approved for use as processing aids in food. No chemical processing aids are employed in the manufacturing process. The oat protein product containing approximately 52-56% protein has been characterized and meets appropriate food grade specifications found.

- There is common knowledge of a long history of human consumption of oats. Numerous food products containing oats are currently marketed in the U.S. and around world and oat protein has become a desirable ingredient for addition to a variety of food products as a source of dietary protein.

- The intended uses of PrOatein® (oat-derived protein) will provide an alternative to other dietary sources of protein as part of the total dietary protein intakes among the U.S. population.

- Epidemiological studies and clinical trials have consistently revealed the cardiovascular benefits of oat consumption from its hypocholesterolemic effects. In 1997, the FDA approved a health claim for the association between oat consumption and coronary heart disease (Katz, 2001; FDA, 1997).

- To date, FDA has reviewed extensive published information and data as part of GRAS notifications for animal and plant-based protein isolates and concentrates and subsequently issued "no questions letters" (e.g., GRN No. 26 (isolated wheat protein); GRN No. 37 (whey protein isolate and dairy product solids); GRN No. 168 (poultry protein); GRN No. 182 (hydrolyzed wheat gluten isolate; pea protein

isolate); GRN No. 313 (beef protein); GRN No. 314 (pork protein); GRN No. 327 (cruciferin-rich canola/rapeseed protein isolate and napin-rich canola/rapeseed protein isolate); GRN 386 (canola protein isolate and hydrolyzed canola protein isolate); GRN No. 447 (potato protein isolates)). Studies in both animal and humans have been evaluated, including a 90-day rat feeding study with a canola protein isolate (min. 90% protein) very similar in amino acid profile to the proposed oat protein product. No toxicity was evident at concentrations up to 20% in the diet. No recent human or animal studies raising any new safety concerns concerning protein or protein isolates and their addition to processed foods have appeared in the published literature subsequent to these evaluations.

- The publicly available scientific literature on oats, oat protein, and other plant-derived protein products and their subsequent utilization as a source of amino acids is sufficient to support the safety and GRAS status of the proposed oat protein product.

Since this safety evaluation was based on generally available and widely accepted data and information, it also satisfies the so-called "common knowledge" element of a GRAS determination.

Determination of the safety and GRAS status of oat protein that is the subject of this assessment has been made through the deliberations of an Expert Panel convened by Tate & Lyle and comprised of Michael Carakostas, DVM, Ph.D., Carol A. Knight, Ph.D., and Stanley M. Tarka, Jr., Ph.D. These individuals are qualified by scientific training and experience to evaluate the safety of substances intended to be added to foods. They have critically reviewed and evaluated the publicly available information summarized in this document and have individually and collectively concluded that oat-derived protein, produced consistent with Good Manufacturing Practice and meeting the specifications described herein, is safe under its intended conditions of use. The Panel further unanimously concludes that these uses of oat protein are GRAS based on scientific procedures, and that other experts qualified to assess the safety of foods and food additives would concur with these conclusions. The Panel's GRAS opinion is included as Exhibit 1 to this document.

It is also Tate & Lyle's opinion that other qualified scientists reviewing the same publicly available toxicological and safety information would reach the same conclusion. Tate & Lyle has concluded that oat protein is GRAS under the intended conditions of use on the basis of scientific procedures; and therefore, it is excluded from the definition of a food additive and may be marketed and sold for its intended purpose in the U.S. without the promulgation of a food additive regulation under Title 21 of the CFR.

Tate & Lyle is not aware of any information that would be inconsistent with a finding that the proposed use of oat protein in food for human consumption meeting appropriate specifications and used according to Good Manufacturing Practice, is GRAS. Recent reviews of the scientific literature revealed no potential adverse health concerns.

## 7.0 References

American Celiac Society. 2014. Recommended Diet - Milk Free /Gluten (Gliadin) Free Diet. Available at http://www.americanceliacsociety.org/diet1.h®l

Anderson OD. 2014. The spectrum of major seed storage genes and proteins in oats (Avena sativa).PLoS One. 9(7):e83569. doi: 10.1371/journal.pone.0083569. eCollection.

Bauer J, Biolo G, Cederholm T, Cesari M, Cruz-Jentoft AJ, Morley J, Phillips S, Sieber C, Stehle P, Teta D, Visvanathan R, Volpi E, Boirie Y. 2013. Evidence-based recommendations for optimal dietary protein intake in older people: a position paper from the PROT-AGE study group. J Am Med Dir Assoc 14(8):542-559.

Boussault P, Léauté-Labrèze C, Saubusse E, Maurice-Tison S, Perromat M, Roul S, Sarrat A, Taïeb A, Boralevi F. 2007. Oat sensitization in children with atopic dermatitis: prevalence, risks and associated factors. Allergy 62(11):1251-6.

Bricker M, Mitchell HH, Kinsman, GM. 1945. The protein requirements of adult human subjects in terms of the protein contained in individual foods and food combinations. J. Nutr. 30:269-283.

Centers for Disease Control and Prevention (CDC). 2014. Nutrition for Everyone: Protein. http://www.cdc.gov/nutrition/everyone/basics/protein.h®l

Cluskey JE, Wu YV, Wall JS, Inglett GE. 1979. Food applications of oat, sorghum, and triticale protein products. J Am Oil Chemists Society 56:481-483.

Comino I, Real A, de Lorenzo L, Cornell H, López-Casado MÁ, Barro F, Lorite P, Torres MI, Cebolla A, Sousa C. 2011. Diversity in oat potential immunogenicity: basis for the selection of oat varieties with no toxicity in coeliac disease. Gut 60(7):915-22.

Davy BM, Davy KP, Ho RC, Beske SD, Davrath LR, Melby CL. 2002. High-fiber oat cereal compared with wheat cereal consumption favorably alters LDL-cholesterol subclass and particle numbers in middle-aged and older men. Am. J. Clin. Nutr. 76(2):351-8.

de Pee S, Bloem MW. 2009. Current and potential role of specially formulated foods and food supplements for preventing malnutrition among 6- to 23-month-old children and for treating moderate malnutrition among 6- to 59-month-old children. Food Nutr. Bull. 30(3 Suppl):S434-63.

Dickey W. 2007. Making oats safer for patients with coeliac disease. Eur. J. Gastroenterol. Hepatol. 20(6):494-5.

Food and Drug Administration (FDA) 1997. Final rule for food labeling: Health claims: Oats and coronary heart disease. Federal Register. 62: 3584–3681.

FDA. 1999. GRAS Notice (GRN) No. 26. GRAS Assessment of Isolated Wheat Protein. Prepared by the Manildra Group. http://www.fda.gov/Food/IngredientsPackagingLabeling/GRAS/NoticeInventory/ucm361097.h®

FDA. 2000. GRN No. 37. GRAS Notification for Whey Protein Isolate and Dairy Product Solids. Prepared by Keller and Heckman, LLP http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-foods-gen/documents/document/ucm266140.pdf

FDA. 2006. GRN No. 182. GRAS Notification for Plant Proteins in Winemaking. Martin Vialatte http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-foods-gen/documents/document/ucm268979.pdf

FDA. 2010. Food Allergies: What You Need to Know. Food Facts. June.

FDA. 2010. GRN No. 327. GRAS Notification for Cruciferin-Rich and Bapin-Rich Protein Isolates Derived fron Canola/Rapeseed (Puratein and Supertein). Prepared by Archer Daniels Midland Co. (ADM) http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-foods-gen/documents/document/ucm269508.pdf

FDA. 2011. GRN No. 386. GRAS Assessment of Canola Protein Isolate and Hydrolyzed Canola Protein Isolate. Prepared by Keller and Heckman, LLP http://www.fda.gov/Food/IngredientsPackagingLabeling/GRAS/NoticeInventory/ucm361097.h®

FDA. 2012. GRN No. 437, GRAS Assessment of Oat β-Glucan - B-CAN® Food Usage Conditions for General Recognition of Safety. Prepared for Garuda, Exeter, CA by McQuate RS and Soni MG.

FDA. 2013. GRN 447. GRAS Assessment of Potato Protein Isolates. Prepared by Solanic B.V. http://www.fda.gov/Food/IngredientsPackagingLabeling/GRAS/NoticeInventory/ucm361097.h®

Freedman AR, Galfre G, Gal E, Ellis HJ, Ciclitira PJ. 1988. Western immunoblotting of cereal proteins with monoclonal antibodies to wheat gliadin to investigate coeliac disease. Int. Arch. Allergy Appl. Immun. 85:34-6350.

Graham GG, MacLean WC Jr, Morales E. 1990. The nutritional value of oat flour for very young children. J. Pediatr. Gastroenterol. Nutr. 10(3):344-50.

Health Canada. 2007. Celiac Disease and the Safety of Oats: Health Canada's Position on the Introduction of Oats to the Diet of Individuals Diagnosed with Celiac Disease (CD). Cat.: H164-51/2007E-PDF, ISBN: 978-0-662-46940-7.

HHS/USDA. 2005. The U.S. Depar®ent of Health and Human Services (HHS) and the U.S. Depar®ent of Agriculture (USDA). Dietary Guidelines for Americans. http://www.health.00v/dietarvouidelines/dqa2005/document/pdf/DGA2005.pdf

Hoffenberg EJ, Haas J, Drescher A, Barnhurst R, Osberg I, Bao F, Eisenbarth G.J. 2000. A trial of oats in children with newly diagnosed celiac disease. Pediatr. 137(3):361-6.

Holm K, Mäki M, Vuolteenaho N, Mustalahti K, Ashorn M, Ruuska T, Kaukinen K. 2006. Oats in the trea®ent of childhood coeliac disease: a 2-year controlled trial and a long-term clinical follow-up study. Aliment. Pharmacol. Ther. 23(10):1463-72.

Institute of Medicine (IOM) of the National Academies. 2005. Dietary, Functional and Total Fiber. Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids Washington DC. National Academies Press.

Katz DL. 2001. A scientific review of the health benefits of oats. The Quaker Oats Company, September 2001.

Kemppainen T, Janatuinen E, Holm K, Kosma VM, Heikkinen M, Mäki M, Laurila K, Uusitupa M, Julkunen R. 2007. No observed local immunological response at cell level after five years of oats in adult coeliac disease. R. Scand. J. Gastroenterol. 42(1):54-9.

Koerner TB, Cléroux C, Poirier C, Cantin I, Alimkulov A, Elamparo H. 2011. Gluten contamination in the Canadian commercial oat supply. Food Addit. Contam. Part A Chem. Anal. Control Expo. Risk Assess. 28(6):705-10.

Koskinen O, Villanen M, Korponay-Szabo I, Lindfors K, Mäki M, Kaukinen K. 2009. Oats do not induce systemic or mucosal autoantibody response in children with coeliac disease. J. Pediatr. Gastroenterol. Nutr. 48(5):559-65.

Kupper C. Gastroenterology. 2005. Dietary guidelines and implementation for celiac disease. 128(4 Suppl 1):S121-7

Lundin KEA, Nilsen EM, Scott HG, Løberg EM, Gjøen A, Bratlie J, Skar V, Mendez E, Løvik A, Kett K. 2003. Oats induced villous atrophy in coeliac disease. Gut. 52(11):1649–1652.

Ma C-Y. 1983. Chemical characterization and functionality assessment of protein concentrates from oats. Cereal Chem 60(1): 36-42.

Maglio M, Mazzarella G, Barone MV, Gianfrani C, Pogna N, Gazza L, Stefanile R, Camarca A, Colicchio B, Nanayakkara M, Miele E, Iaquinto G, Giardullo N, Maurano F,

Santoro P, Troncone R, Auricchio S. 2011. Immunogenicity of two oat varieties, in relation to their safety for celiac patients. Scand. J. Gastroenterol. 46(10):1194-205.

Martin WF, Armstrong LE, Rodriguez NR. 2005. Dietary protein intake and renal function. Nutr. Metab. (Lond). 2(25). doi:10.1186/1743-7075-2-25.

National Foundation for Celiac Awareness (NFCA). 2014. The Gluten-Free Diet. Available at http://www.celiaccentral.org/Gluten-Free-Food/the-gluten-free-diet/

Nesterenko A, Alric I, Silvestre F, Durrieu V. 2013. Vegetable proteins in microencapsulation: a review of recent interventions and their effectiveness. Ind. Crop. Prod. 42:469-479.

Oats and Health. 2014. Oat Protein. http://www.oatsandhealth.org/composition-oats-and-health-27/oat-protein

Pariza MW, Johnson EA. 2001. Evaluating the safety of microbial enzyme preparations used in food processing: update for a new century. Regul. Toxicol. Pharmacol. 33(2):173-86.

Pulido OM, Gillespie Z, Zarkadas M, Dubois S, Vavasour E, Rashid M, Switzer C, Godefroy SB. 2009. Introduction of oats in the diet of individuals with celiac disease: a systematic review. Adv. Food Nutr. Res.57:235-85.

Rashid M, Butzner D, Burrows V, Zarkadas M, Case S, Molloy M, Warren R, Pulido O, Switzer C. 2007. Consumption of pure oats by individuals with celiac disease: a position statement by the Canadian Celiac Association. Can. J. Gastroenterol. 21(10):649-51.

Real A, Comino I, de Lorenzo L, Merchan F, Gil-Humanes J, Gimenez MJ, Lopez-Casado MA, Torres MI, Cebolla A, Sousa C, Barro F, Pistom F. 2012. Molecular and immunological characterization of gluten proteins isolated from oat cultivars that differ in toxicity for celiac disease. PLoS ONE 7(12):e48365.

Reunala T, Collin P, Holm K, Pikkarainen P, Miettinen A, Vuolteenaho N, Mäki M. 1998. Tolerance to oats in dermatitis herpetiformis. Gut. 43(4):490-3.

Richman E. 2012. The safety of oats in the dietary trea®ent of coeliac disease. Conference on 'Malnutrition matters' Symposium 1: Living with coeliac disease. Proc. Nutr. Soc. 71(4):534-7.

Sey MS, Parfitt J, Gregor J. 2011. Prospective study of clinical and histological safety of pure and uncontaminated Canadian oats in the management of celiac disease. J. Parenter. Enteral. Nutr. 35(4):459-64.

Sherman HC, Winters JC, Phillips V. 1919. Efficiency of Oat Protein in Adult Human Nutrition. J. Biol. Chem. 1919, 39:53-62.

Silano M, Pozo EP, Uberti F, Manferdelli S, Del Pinto T, Felli C, Budelli A, Vincentini O, Restani P. 201. Diversity of oat varieties in eliciting the early inflammatory events in celiac disease. Eur J Nutr. Aug;53(5):1177-86.

Sjoberg V, Hollen E, Pietz G, Magnusson K-E, Falth-Magnusson K, Sundstrom M, Peterson KH, Sandstrom O, Hernell O, Hammarstrom S, Hogberg L, Hammarstrom ML. 2014. Noncontaminated dietary oats may hamper normalization of the intestinal immune status in childhood celiac disease. Citation: Clin. Translat. Gastroenterol. 5, e58; doi:10.1038/ctg.2014.9.

Thompson T. 1997. Do oats belong in a gluten-free diet? J. Am. Diet Assoc. 97(12):1413-6.

Troncone R, Auricchio S, De Vincenzi M, Donatiello A, Farris E, Silano V. 1987. J. An analysis of cereals that react with serum antibodies in patients with coeliac disease. Pediatr. Gastroenterol. Nutr. 6(3):346-50.

Tsopmo A, Cooper A, Jodayree IS. 2010. Enzymatic hydrolysis of oat flour protein isolates to enhance antioxidative properties. Adv. J. Food Sci. Tech. 2(4): 206-212.

US Depar®ent of Agriculture (USDA). 2014. MyPlate. http://www.choosemyplate.gov/about.h®l

Wang P, Chen H, Zhu Y, McBride J, Fu J, Sang S. 2015 . Oat avenanthramide-C (2c) is biotransformed by mice and the human microbiota into bioactive metabolites. J. Nutr. 145(2):239-45. doi: 10.3945/jn.114.206508.

World Health Organization (WHO). 2002. Technical Report Series 935: Protein and Amino Acid Requirements in Human Nutrition. Report of a Joint WHO/FAO/UNU Expert Consultation.

Wu YV, Sexson KR, Cavins JF, Inglett GE. 1972. Oats and their dry-milled fractions: Protein isolation and properties of four varieties. J. Agric. Food Chem. 20(4):757–761.

Zhou AL, Hergert N, Rompato G, Lefevre M. 2015. Whole grain oats improve insulin sensitivity and plasma cholesterol profile and modify gut microbiota composition in C57BL/6J mice. J. Nutr. 145(2):222-30. doi: 10.3945/jn.114.199778.

# 8.0 Appendices



42

# Appendix A. Certificates of Analysis – Characterization



43

eurofins

Rapport utfärdad av ackrediterat laboratorium

Report issued by Accredited Laboratory

**Eurofins Food & Agro Testing Sweden AB**
Box 887
Sjöhagsg. 3
SE-53119 Lidköping
www.eurofins.se

Tlf: +46 10 490 8310

Tate&Lyle Sweden AB
Ingbritt Johansson
Älvåsvägen 1
610 20 KIMSTAD

**AR-14-LW-018536-01**

**EUSELI-00064732**

Kundnummer: LW9901581

# Analysrapport

Provnummer: **525-2014-04280071**
Provmärkning: Havre B.04 04 14 oat
Provet ankom: 2014-04-28
Analysrapport klar: 2014-05-08
Analyserna påbörjades: 2014-04-28

| | Analys | Resultat | MRL | Enhet | Måto. | Metod/ref | Lab |
|---|---|---|---|---|---|---|---|
| LW00V | Råfett enl. Soxtec (FAT) | 3.83 | | g/100 g | ± 10% | | EUSELI |
| SL403 | Bly Pb | < 0.020 | | mg/kg | ± 20% | NMKL No 161 1998 mod | EUSELI2 |
| SL404 | Kadmium Cd | 0.015 | | mg/kg | ± 20% | NMKL No 161 1998 mod | EUSELI2 |
| SL402 | Arsenik As | < 0.050 | | mg/kg | ± 35% | NMKL No 161 1998 mod | EUSELI2 |
| SL399 | Kvicksilver Hg | < 0.020 | | mg/kg | ± 30% | SS-EN 16277:2012 | EUSELI2 |
| JJ006 | Aflatoxin B1 | <0.1 | | µg/kg | | EN 14123, mod. | EUHAWE3 |
| JJ006 | Aflatoxin B2 | <0.1 | | µg/kg | | EN 14123, mod. | EUHAWE3 |
| JJ006 | Aflatoxin G1 | <0.1 | | µg/kg | | EN 14123, mod. | EUHAWE3 |
| JJ006 | Aflatoxin G2 | <0.1 | | µg/kg | | EN 14123, mod. | EUHAWE3 |
| LW020 | Ochratoxin | <0.10 | | µg/kg | ± 30% | NMKL 143 | EUSELI |
| LW03Z | Deoxynivalenol (DON) | 220 | | µg/kg | ± 25% | In house metod (210) | EUSELI |
| LW03X | HT-2 Toxin | 14 | | µg/kg | ± 30% | In house metod (210) | EUSELI |
| LW03Y | T-2 Toxin | <10 | | µg/kg | ± 30% | In house metod (210) | EUSELI |
| LW041 | Zearalenone (ZON) | <10 | | µg/kg | ± 35% | In house metod (210) | EUSELI |
| MJ011 | Stärkelse inkl. enkla sockerarter (starch + sugar) | 42 | | g/100 g | | Intern metod | EUNDTR2 |

LP130: Inga pesticidrester påvisade (SLV K:-f4-m016.1). Not detected

Per-Olov Södergren, Rapportansvarig

Denna rapport är elektroniskt signerad.

Måto: Mätosäkerhet

Förklaringar: AR-004 v21

* : Ej ackrediterad analys

Utförande laboratorium om inte annat anges: Eurofins Food & Agro (Lidköping)

Denna rapport får endast återges i sin helhet, om inte utförande laboratorium skriftligen godkänt annat. Resultaten relaterar endast till det

Lantmännen

27/02/2015 Malmö

Lantmännen ek för

205 03 Malmö

## Letter of Declaration

We Lantmännen as supplier of oats to Tate&Lyle Sweden AB hereby certify all oats delivered is in accordance with regulation EU 1881.2006 for unprocessed cereals – setting maximum levels for certain contaminants in foodstuff.

Regards

(b) (6)

Göran Karlsson
Product Manager

Lantmännen ek för

Lantmännen
Visiting address
St: Göransgatan 160 A
104 92 Stockholm
Box 30192
104 25 Stockholm
Tel. 010-556 00 00
E-mail info@lantmannen.com
www.lantmannen.com
Company ID 769605-2856 Registered office
VAT no. SE769605265601 Stockholm

TATE & LYLE

# CERTIFICATE OF ANALYSIS

**Product:** 200 200 prOATein™

**Batch no:** 1332

**Prod. Date:** 06-08-2013

**Exp.Date:** 05-08-2014

| Chemical analysis | Result | Unit | Method |
|---|---|---|---|
| Average value | | | |
| Protein (N*6,25) | 52,9 | % | IDF 20B Kjeldahl |
| Dry matter | 95,8 | % | IDF Standard method |
| **Bacteriological analysis** | | | |
| Total plate count | <1000 | cfu/g | NMKL Nr 86, 1999 |
| Enterobacteriaceae | <10 | cfu/g | NMKL Nr 144, 2000 |
| Staph.aureus | <20 | cfu/g | NMKL Nr 66 3 edt.1999 modified |
| Yeast | <20 | cfu/g | IDF 94B modified |
| Moulds | <20 | cfu/g | IDF 94B modified |
| Salmonella | Neg/25g. | | NMKL Nr 71 5 edt. Modified |
| E.coli cfu/g | Negative | | NMKL nr 125, 3edt.1996 |

**Tate&Lyle Sweden AB**
**28-09-2014**

(b) (6)

Ingbritt Johansson
Quality Manager

eurofins
eurofins

Rapport utfärdad av ackrediterat laboratorium

Report issued by Accredited Laboratory

**Eurofins Food & Agro Testing Sweden AB**
Box 887
Sjöhagsg. 3
SE-53119 Lidköping
www.eurofins.se

Tlf: +46 10 490 8310

Tate&Lyle Sweden AB
Ingbritt Johansson
Älvåsvägen 1
610 20 KIMSTAD

**AR-13-LW-031352-01**
**EUSELI-00047711**
Kundnummer: LW9901581

# Analysrapport

Provnummer: 525-2013-08190021
Provmärkning: prOATein Oatprotein Batch 1332
Provet ankom: 2013-08-19
Analyserna påbörjades: 2013-08-19

Ej Validerad

| | Analys | Resultat | MRL | Enhet | Mätn. | Metod/ref | Lab |
|---|---|---|---|---|---|---|---|
| SL408 | Kalcium Ca | **1400** | | mg/kg | ± 10% | NMKL No 139 1991 mod | *EUSELI2* |
| SL411 | Magnesium Mg | **2300** | | mg/kg | ± 10% | NMKL No 139 1991 mod | *EUSELI2* |
| SL413 | Järn Fe | **48** | | mg/kg | ± 10% | NMKL No 139 1991 mod | *EUSELI2* |
| SL410 | Kalium K | **3200** | | mg/kg | ± 15% | NMKL No 139 1991 mod | *EUSELI2* |
| SL409 | Fosfor P | **8200** | | mg/kg | ± 10% | NMKL No 139 1991 mod | *EUSELI2* |
| SL416 | Bor B | **< 5.0** | | mg/kg | ± 20% | NMKL No 161 1998 mod | *EUSELI2* |
| SL415 | Zink Zn | **61** | | mg/kg | ± 10% | NMKL No 139 1991 mod | *EUSELI2* |
| SL400 | Jod I | **<0.10** | | mg/kg | ± 35% | SS-EN 15111:2007 | *EUSELI2* |
| SL403 | Bly Pb | **< 0.020** | | mg/kg | ± 20% | NMKL No 161 1998 mod | *EUSELI2* |
| SL404 | Kadmium Cd | **0.052** | | mg/kg | ± 20% | NMKL No 161 1998 mod | *EUSELI2* |
| SL402 | Arsenik As | **< 0.050** | | mg/kg | ± 35% | NMKL No 161 1998 mod | *EUSELI2* |
| SL399 | Kvicksilver Hg | **< 0.020** | | mg/kg | ± 30% | SS-EN 16277:2012 | *EUSELI2* |
| A0428 | Aflatoxin B1 | **<0.01** | | µg/kg | | EN 15851, mod. | *EUHAWE3* |
| A0428 | Aflatoxin B2 | **<0.01** | | µg/kg | | EN 15851, mod. | *EUHAWE3* |
| A0428 | Aflatoxin G1 | **<0.01** | | µg/kg | | EN 15851, mod. | *EUHAWE3* |
| A0428 | Aflatoxin G2 | **<0.01** | | µg/kg | | EN 15851, mod. | *EUHAWE3* |
| LW020 | Ochratoxin | **0.24** | | µg/kg | ± 30% | NMKL 143 | *EUSELI* |
| LW032 | Deoxynivalenol (DON) | **25** | | µg/kg | ± 25% | In house metod (210) | *EUSELI* |
| LW041 | Zearalenone (ZON) | **<10** | | µg/kg | ± 25% | In house metod (210) | *EUSELI* |
| JJ0BG | Fumonisin B1 (FB1) | **<20** | | µg/kg | | Internal method | *EUHAWE3* |
| JJ0BG | Fumonisin B2 (FB2) | **<20** | | µg/kg | | Internal method | *EUHAWE3* |

Mätn: Mätosäkerhet

Förklaringar
*: Ej ackrediterad analys
Utförande laboratorium om inte annat anges: Eurofins Food & Agro (Lidköping)

AR-004 v21

Denna rapport får endast återges i sin helhet, om inte utförande laboratorium i förväg skriftligen godkänt annat. Resultaten relaterar endast till det undersökta provet.



47

47

000057

eurofins

AR-13-LW-031352-01

EUSELI-00047711

| | | | | | | |
|---|---|---|---|---|---|---|
| LP130 | DMST | 0.024 | mg/kg | | SLV K1-f4-m016.1 | *EUSELI* |
| SLB89 | Svavel S | 7300 | mg/kg | ± 20% | NMKL No 161 1998 moc | *EUSELI2* |

LP130. För övrigt inga pesticidrester påvisade (SLV K1-f4-m016.1).

**Rapportkommentar:**
Eventuella pesticidrester har matosäkerhet i intervallet 30-60%.

Per-Olov Södergren, Rapportansvarig

**Utförande Laboratorium**

| | |
|---|---|
| *EUHAWE3* | Eurofins WEJ Contaminants GmbH (Hamburg) |
| *EUSELI* | Eurofins Food & Agro Testing Sweden AB, Lidköping |
| *EUSELI2* | Eurofins Environment Sweden, Lidköping |

Moc: Matosäkerhet

Förklaringar AR-004 v21

- : Ej ackrediterad analys

Utförande laboratorium om inte annat anges: Eurofins Food & Agro (Lidköping)

Denna rapport får endast återges i sin helhet, om inte utförande laboratorium i förväg skriftligen godkänt annat. Resultaten relaterar endast till det ovanstående provet.



*Analysis of crude protein was not conducted by Eurofins on batch number 1332.



48

# TATE & LYLE

## CERTIFICATE OF ANALYSIS

**Product:** 200 200 prOATein™

**Batch no:** 1411

**Prod. Date:** 14-03-2014

**Exp.Date:** 13-03-2015

| Chemical analysis | Result | Unit | Method |
|---|---|---|---|
| Average value | | | |
| Protein (N*6,25) | 55 | % | IDF 20B Kjeldahl |
| Dry matter | 96,7 | % | IDF Standard method |

**Bacteriological analysis**

| | | | |
|---|---|---|---|
| Total plate count | <1000 | cfu/g | NMKL Nr 86, 1999 |
| Enterobacteriaceae | <10 | cfu/g | NMKL Nr 144, 2000 |
| Staph.aureus | <20 | cfu/g | NMKL Nr 66 3 edt.1999 modified |
| Yeast | <20 | cfu/g | IDF 94B modified |
| Moulds | <60 | cfu/g | IDF 94B modified |
| Salmonella | Neg/25g. | | NMKL Nr 71 5 edt. Modified |
| E.coli cfu/g | Negative | | NMKL nr 125, 3edt.1996 |

**Tate&Lyle Sweden AB**
**28-09-2014**
(b) (6)

Ingbritt Johansson
Quality Manager

eurofins

Rapport utfärdad av ackrediterat laboratorium

Report issued by Accredited Laboratory

Eurofins Food & Agro Testing Sweden AB
Box 887
Sjöhagsg. 3
SE-53119 Lidköping
www.eurofins.se

Tlf: +46 10 490 8310

Tate&Lyle Sweden AB
Ingbritt Johansson
Alvåsvägen 1
610 20 KIMSTAD

**AR-14-LW-050173-01**

**EUSELI-00080887**

Client code:: LW9901581

# ANALYTICAL REPORT

Sample code: 525-2014-11200147
Client Sample: PrOatein 1411
Received: 2014-11-20
Report finished: 2014-12-03
Start of analysis 2014-11-20 13:27:18

| | Analysis | Result: Unit | Uncert. | Method | Lab |
|---|---|---|---|---|---|
| LP021 | Crude Protein Kjeldahl (Nx6,25) | 53.1 g/100 g | ± 10% | NMKL 6 | *EUSELI* |
| LP06X | Fat acc. SBR mod. | 17.4 g/100 g | ± 10% | SLV VF 1980 | *EUSELI* |
| SL412 | Sodium (Na) | 95 mg/kg | ± 25% | NMKL No 139 1991 mod | *EUSELI2* |
| SL408 | Calcium (Ca) | 1200 mg/kg | ± 10% | NMKL No 139 1991 mod | *EUSELI2* |
| SL411 | Magnesium (Mg) | 1700 mg/kg | ± 10% | NMKL No 139 1991 mod | *EUSELI2* |
| SL413 | Iron (Fe) | 42 mg/kg | ± 10% | NMKL No 139 1991 mod | *EUSELI2* |
| SL410 | Potassium (K) | 2500 mg/kg | ± 15% | NMKL No 139 1991 mod | *EUSELI2* |
| SL409 | Phosphorus (P) | 6900 mg/kg | ± 10% | NMKL No 139 1991 mod | *EUSELI2* |
| SL418 | * Boron (B) | <5.0 mg/kg | ± 20% | NMKL No 181 1998 mod | *EUSELI2* |
| SL415 | Zinc (Zn) | 66 mg/kg | ± 10% | NMKL No 139 1991 mod | *EUSELI2* |
| JJ006 | Aflatoxin B1 | <0.1 µg/kg | | internal method based on EN 14123 | *EUHAWE3* |
| JJ006 | Aflatoxin B2 | <0.1 µg/kg | | internal method based on EN 14123 | *EUHAWE3* |
| JJ006 | Aflatoxin G1 | <0.1 µg/kg | | internal method based on EN 14123 | *EUHAWE3* |
| JJ006 | Aflatoxin G2 | <0.1 µg/kg | | internal method based on EN 14123 | *EUHAWE3* |
| LW020 | Ochratoxin | 0.17 µg/kg | ± 30% | NMKL 143 | *EUSELI* |
| LW03Z | Deoxynivalenol (Vomitoxin ) | 18 µg/kg | ± 25% | In house method (210) | *EUSELI* |
| LW041 | Zearalenone (ZON) | <10 µg/kg | ± 35% | In house method (210) | *EUSELI* |
| JJ08G | Fumonisin B1 (FB1) | <20 µg/kg | | Internal method | *EUHAWE3* |
| JJ08G | Fumonisin B2 (FB2) | <20 µg/kg | | Internal method | *EUHAWE3* |
| J1071 | Iodine | <0.2 mg/kg | | Sandell-Kolthoff | *EUHAWE3* |
| MJ011 | Starch and sugar | 14 g/100 g | | Internal method | *EUNOTR2* |
| SL869 | Sulphur total (S) | 6900 mg/kg | ± 20% | NMKL No 161 1998 mod | *EUSELI2* |

The laboratory/laboratories are accredited by the respective national accreditation body. Non-accredited tests are marked *.

Symbol description:
* Not accredited

AR-003 v78
1.67 130516

Uncert: Measurement uncertainty

Measurement uncertainty, unless otherwise stated, are reported as expanded uncertainty with coverage factor 2. Exceptions related to analysis performed outside Sweden may occur. Additional information can be obtained upon request.





50

50

000060

Per-Olov Södergren, ASM

This test report has been created electronically and has been verified and authorised.

**Test was performed by**

| | |
|---|---|
| *EUHAWE3* | Eurofins WEJ Contaminants GmbH (Hamburg) |
| *EUNOTR2* | Eurofins Food & Agro Testing Norway AS (Skansen), Trondheim |
| *EUSELI* | Eurofins Food & Agro Testing Sweden AB, Lidköping |
| *EUSELI2* | Eurofins Environment Sweden, Lidköping |

The laboratory/laboratories are accredited by the respective national accreditation body. Non-accredited tests are marked *.

Symbol description:
* Not accredited

AR-003 v78
1.67 130516

Uncert: Measurement uncertainty

Measurement uncertainty, unless otherwise stated, are reported as expanded uncertainty with coverage factor 2. Exceptions related to analysis performed outside Sweden may occur. Additional information can be obtained upon request.

eurofins

**Eurofins Food & Agro Testing Sweden AB**
Box 887
Sjöhagsg. 3
SE-53119 Lidköping
www.eurofins.se

Tfn: +46 10 490 8310

Tate&Lyle Sweden AB
Ingbritt Johansson
Älvåsvägen 1
610 20 KIMSTAD

**AR-14-LW-043082-01**

**EUSELI-00076399**

Kundnummer: LW9901581

# Analysrapport

| | |
|---|---|
| Provnummer: | 525-2014-10010201 |
| Provmärkning: | PrOatein Batch 1411 |
| Provet ankom: | 2014-10-01 |
| Analysrapport klar: | 2014-10-13 |
| Analyserna påbörjades: | 2014-10-01 14:36:54 |

| | Analys | Resultat | Enhet | Mätn. | Metod/ref | Lab |
|---|---|---|---|---|---|---|
| SL403 | Bly Pb | <0.020 | mg/kg | ± 20% | NMKL No 161 1998 mod | *EUSELI2* |
| SL404 | Kadmium Cd | 0.11 | mg/kg | ± 20% | NMKL No 161 1998 mod | *EUSELI2* |
| SL402 | Arsenik As | <0.050 | mg/kg | ± 35% | NMKL No 161 1998 mod | *EUSELI2* |
| SL399 | Kvicksilver Hg | < 0.020 | mg/kg | ± 30% | SS-EN 16277:2012 | *EUSELI2* |

Per-Olov Södergren, Rapportansvarig

Denna rapport är elektroniskt signerad.

**Utförande Laboratorium**

*EUSELI2* Eurofins Environment Sweden, Lidköping

Laboratoriet/laboratorierna är ackrediterade av respektive lands ackrediteringsorgan. Ej ackrediterade analyser är markerade med *

Förklaringar
* Ej ackrediterad analys

AR-003 v78
1.67 130516

Mätn: Mätosäkerhet

Mätosäkerheten, om inget annat anges, redovisas som utvidgad mätosäkerhet med täckningsfaktor 2. Undantag relaterat till analyser utförda utanför Sverige kan förekomma. Ytterligare upplysningar kan lämnas på begäran. Upplysning om mätosäkerhet och detektionsnivåer för mikrobiologiska analyser lämnas på begäran.

eurofins

Rapport utfärdad av ackrediterat laboratorium

Report issued by Accredited Laboratory

SWEDAC ACKREDITERING

**Eurofins Food & Agro Testing Sweden AB**
Box 887
Sjöhagsg. 3
SE-53119 Lidköping
www.eurofins.se

Tlf: +46 10 490 8310

Tate&Lyle Sweden AB
Ingbritt Johansson
Älvåsvägen 1
610 20 KIMSTAD

**AR-14-LW-054885-01**

**EUSELI-00083017**

Client code:: LW9901581

# ANALYTICAL REPORT

| | |
|---|---|
| Sample code: | **525-2014-12120146** |
| Client Sample: | Proatein 1411 |
| Received: | 2014-12-12 |
| Report finished: | 2014-12-17 |
| Start of analysis | 2014-12-12 |

| Analysis | Result | MRL | Unit | Uncert. | Method | Lab |
|---|---|---|---|---|---|---|
| LP130: No pesticide residue detected (SLV K1-f4-m016.1). | | | | | | |

Per-Olov Södergren, ASM

This test report has been created electronically and has been verified and authorised.

**Test was performed by**

*EUSELI* Eurofins Food & Agro Testing Sweden AB, Lidköping

Uncert: Measurement uncertainty

Symbol description:
+ : (Not part of the accreditation)

AR-004 v22

Performing laboratory if nothing else is stated: Eurofins Food & Agro (Lidköping)

TATE & LYLE

# CERTIFICATE OF ANALYSIS

**Product:** 200 200 prOATein™

**Batch no:** 1413

**Prod. Date:** 31-03-2014

**Exp.Date:** 30-03-2015

| Chemical analysis | Result | Unit | Method |
|---|---|---|---|
| Average value | | | |
| Protein (N*6,25) | 56 | % | IDF 20B Kjeldahl |
| Dry matter | 95,5 | % | IDF Standard method |
| **Bacteriological analysis** | | | |
| Total plate count | <1000 | cfu/g | NMKL Nr 86, 1999 |
| Enterobacteriaceae | <10 | cfu/g | NMKL Nr 144, 2000 |
| Staph.aureus | <20 | cfu/g | NMKL Nr 66 3 edt.1999 modified |
| Yeast | <20 | cfu/g | IDF 94B modified |
| Moulds | <20 | cfu/g | IDF 94B modified |
| Salmonella | Neg/25g. | | NMKL Nr 71 5 edt. Modified |
| E.coli cfu/g | Negative | | NMKL nr 125, 3edt.1996 |

**Tate&Lyle Sweden AB**
**28-09-2014**

(b) (6)

Ingbritt Johansson
Quality Manager

eurofins

Rapport utfärdad av ackrediterat laboratorium

Report issued by Accredited Laboratory

**Eurofins Food & Agro Testing Sweden AB**
Box 887
Sjöhagsg. 3
SE-53119 Lidköping
www.eurofins.se

Tlf: +46 10 490 8310

Tate&Lyle Sweden AB
Ingbritt Johansson
Älvåsvägen 1
610 20 KIMSTAD

**AR-14-LW-022881-01**

**EUSELI-00064747**

Client code:: LW9901581

# ANALYTICAL REPORT

| | |
|---|---|
| Sample code: | **S25-2014-04280096** |
| Client Sample: | PrOstein 1413 |
| Received: | 2014-04-28 |
| Report finished: | 2014-05-26 |
| Start of analysis | 2014-04-28 |

| | | Analysis | Result: | MRL | Unit | Uncert. | Method | Lab |
|---|---|---|---|---|---|---|---|---|
| LP021 | | Crude Protein Kjeldahl (Nx6,25) | 55.2 | | g/100 g | ± 10% | NMKL 6 | *EUSELI* |
| LW00V | | Fat acc. Soxtec | 17.2 | | g/100 g | ± 10% | | *EUSELI* |
| SL412 | | Sodium (Na) | 120 | | mg/kg | ± 25% | NMKL No 139 1991 mod | *EUSELI2* |
| SL408 | | Calcium (Ca) | 1200 | | mg/kg | ± 10% | NMKL No 139 1991 mod | *EUSELI2* |
| SL411 | | Magnesium (Mg) | 1600 | | mg/kg | ± 10% | NMKL No 139 1991 mod | *EUSELI2* |
| SL413 | | Iron (Fe) | 38 | | mg/kg | ± 10% | NMKL No 139 1991 mod | *EUSELI2* |
| SL410 | | Potassium (K) | 2600 | | mg/kg | ± 15% | NMKL No 139 1991 mod | *EUSELI2* |
| SL409 | | Phosphorus (P) | 6800 | | mg/kg | ± 10% | NMKL No 139 1991 mod | *EUSELI2* |
| SL418 | * | Boron (B) | < 5.0 | | mg/kg | ± 20% | NMKL No 161 1998 mod | *EUSELI2* |
| SL415 | | Zinc (Zn) | 59 | | mg/kg | ± 10% | NMKL No 139 1991 mod | *EUSELI2* |
| SL400 | * | Iodine (I) | <0.10 | | mg/kg | ± 35% | EN 15111:2007 | *EUSELI2* |
| SL403 | | Lead (Pb) | < 0.020 | | mg/kg | ± 20% | NMKL No 161 1998 mod | *EUSELI2* |
| SL404 | | Cadmium (Cd) | 0.059 | | mg/kg | ± 20% | NMKL No 161 1998 mod | *EUSELI2* |
| SL402 | | Arsenic (As) | < 0.050 | | mg/kg | ± 35% | NMKL No 161 1998 mod | *EUSELI2* |
| SL399 | | Mercury (Hg) | < 0.020 | | mg/kg | ± 30% | EN 16277:2012 | *EUSELI2* |
| JJ006 | | Aflatoxin B1 | <0.1 | | µg/kg | | internal method based on EN 14123 | *EUHAWE3* |
| JJ006 | | Aflatoxin B2 | <0.1 | | µg/kg | | internal method based on EN 14123 | *EUHAWE3* |
| JJ006 | | Aflatoxin G1 | <0.1 | | µg/kg | | internal method based on EN 14123 | *EUHAWE3* |
| JJ006 | | Aflatoxin G2 | <0.1 | | µg/kg | | internal method based on EN 14123 | *EUHAWE3* |

Uncert: Measurement uncertainty

Symbol description:

AR-004 v21

*: (Not part of the accreditation)

Performing laboratory if nothing else is stated: Eurofins Food & Agro (Lidköping)

| | | | | | | |
|---|---|---|---|---|---|---|
| LW020 | Ochratoxin | <0.10 | µg/kg | ± 30% | NMKL 143 | *EUSELI* |
| LW03Z | Deoxynivalenol (Vomitoxin ) | <10 | µg/kg | ± 25% | In house method (210) | *EUSELI* |
| LW041 | Zearalenone (ZON) | <10 | µg/kg | ± 35% | In house method (210) | *EUSELI* |
| JJ0BG | Fumonisin B1 (FB1) | <20 | µg/kg | | Internal method | *EUHAWE3* |
| JJ0BG | Fumonisin B2 (FB2) | <20 | µg/kg | | Internal method | *EUHAWE3* |
| LP130 | Diphenylamine | 0.014 | mg/kg | | SLV K1-M-m016.1 | *EUSELI* |
| MJ011 | Starch and sugar | 13 | g/100 g | | Internal method | *EUNOTR2* |
| SLB89 | Sulphur total (S) | 8000 | mg/kg | ± 20% | NMKL No 161 1998 mod | *EUSELI2* |

LP130: No other pesticide residues detected (SLV K1-M-m016.1).

Per-Olov Södergren, ASM

This test report has been created electronically and has been verified and authorised.

**Test was performed by**

| | |
|---|---|
| *EUHAWE3* | Eurofins WEJ Contaminants GmbH (Hamburg) |
| *EUNOTR2* | Eurofins Food & Agro Testing Norway AS (Skansen), Trondheim |
| *EUSELI* | Eurofins Food & Agro Testing Sweden AB, Lidköping |
| *EUSELI2* | Eurofins Environment Sweden, Lidköping |

Uncert: Measurement uncertainty

Rapport utfärdad av ackrediterat laboratorium

Report issued by Accredited Laboratory

**Eurofins Food & Agro Testing Sweden AB**
Box 887
Sjöhagsg. 3
SE-53119 Lidköping
www.eurofins.se

Tlf: +46 10 490 8310

Tate&Lyle Sweden AB
Ingbritt Johansson
Älvåsvägen 1
610 20 KIMSTAD

**AR-13-LW-032664-01**

**EUSELI-00048231**

Client code:: LW9901581

# ANALYTICAL REPORT

| | |
|---|---|
| Sample code: | 525-2013-08270167 |
| Client Sample: | prOATein oatprotein Batch1334 GI |
| Received: | 2013-08-27 |
| Report finished: | 2013-09-09 |
| Start of analysis | 2013-08-28 08:43:20 |

| | Analysis | Result: Unit | Uncert. | Method | Lab |
|---|---|---|---|---|---|
| LP021 | Crude Protein Kjeldahl (Nx6,25) | 50.8 g/100 g | ± 10% | NMKL 6 | *EUSELI* |
| LP00W | Alanine | 22.3 g/kg | ± 8% | ISO 13903:2005 | *EUSELI* |
| LP00W | Arginine | 36.0 g/kg | ± 8% | ISO 13903:2005 | *EUSELI* |
| LP00W | Aspartic acid (Total) | 38.6 g/kg | ± 8% | ISO 13903:2005 | *EUSELI* |
| LP00W | Cystine | 10.0 g/kg | ± 8% | ISO 13903:2005 | *EUSELI* |
| LP00W | Phenylalanine | 29.3 g/kg | ± 8% | ISO 13903:2005 | *EUSELI* |
| LP00W | Glutamic Acid | 115.4 g/kg | ± 8% | ISO 13903:2005 | *EUSELI* |
| LP00W | Glycine | 21.4 g/kg | ± 8% | ISO 13903:2005 | *EUSELI* |
| LP00W | Histidine | 11.2 g/kg | ± 8% | ISO 13903:2005 | *EUSELI* |
| LP00W | Hydroxyprolin | <0.1 g/kg | ± 8% | ISO 13903:2005 | *EUSELI* |
| LP00W | Isoleucine | 23.5 g/kg | ± 8% | ISO 13903:2005 | *EUSELI* |
| LP00W | Leucine | 40.9 g/kg | ± 8% | ISO 13903:2005 | *EUSELI* |
| LP00W | Lysine | 17.4 g/kg | ± 8% | ISO 13903:2005 | *EUSELI* |
| LP00W | Methionine | 9.1 g/kg | ± 8% | ISO 13903:2005 | *EUSELI* |
| LP00W | Ornithine | 0.2 g/kg | ± 8% | ISO 13903:2005 | *EUSELI* |
| LP00W | Proline | 27.2 g/kg | ± 8% | ISO 13903:2005 | *EUSELI* |
| LP00W | Serine | 20.7 g/kg | ± 8% | ISO 13903:2005 | *EUSELI* |
| LP00W | Threonine | 15.3 g/kg | ± 8% | ISO 13903:2005 | *EUSELI* |
| LP00W | Tyrosine | 19.7 g/kg | ± 8% | ISO 13903:2005 | *EUSELI* |
| LP00W | Valine | 30.9 g/kg | ± 8% | ISO 13903:2005 | *EUSELI* |
| LP00W | Sum of amino-acids | 489.1 g/kg | | ISO 13903:2005 | *EUSELI* |
| LP00W | Ammonia (NH3) | 14.3 g/kg | ± 8% | ISO 13903:2005 | *EUSELI* |
| LP056 | C 6:0 (Caproic acid) | <0.1 % of fatty acids | ± 20% | GC-FID | *EUSELI* |

The laboratory/laboratories are accredited by the respective national accreditation body. Non-accredited tests are marked *.

Symbol description:
* Not accredited

AR-003 v77
1.67 130516

Uncert: Measurement uncertainty

Measurement uncertainty, unless otherwise stated, are reported as expanded uncertainty with coverage factor 2. Exceptions related to analysis performed outside Sweden may occur. Additional information can be obtained upon request.

| | | | | | |
|---|---|---|---|---|---|
| LP056 | C 8:0 (Caprylic acid) | <0.1 % of fatty acids | ± 20% | GC-FID | EUSELI |
| LP056 | C 10:0 (Capric acid) | <0.1 % of fatty acids | ± 20% | GC-FID | EUSELI |
| LP056 | C 12:0 (Lauric acid) | <0.1 % of fatty acids | ± 20% | GC-FID | EUSELI |
| LP056 | C 14:0 (Myristic acid) | 0.2 % of fatty acids | ± 20% | GC-FID | EUSELI |
| LP056 | C 14:1 (Myristoleic acid) | <0.1 % of fatty acids | ± 20% | GC-FID | EUSELI |
| LP056 | C 15:0 (Pentadecanoic acid) | <0.1 % of fatty acids | ± 20% | GC-FID | EUSELI |
| LP056 | C 15:1 n-5 | <0.1 % of fatty acids | ± 20% | GC-FID | EUSELI |
| LP056 | C 16:0 (Palmitic acid) | 16.2 % of fatty acids | ± 10% | GC-FID | EUSELI |
| LP056 | C 16:1 (Palmitoleic acid) | 0.2 % of fatty acids | ± 20% | GC-FID | EUSELI |
| LP056 | C 17:0 (Margaric acid) | <0.1 % of fatty acids | ± 20% | GC-FID | EUSELI |
| LP056 | C 17:1 n-7 (Heptadecenoic acid) | <0.1 % of fatty acids | ± 20% | GC-FID | EUSELI |
| LP056 | C 18:0 (Stearic acid) | 1.5 % of fatty acids | ± 20% | GC-FID | EUSELI |
| LP056 | C 18:1 n-9 (Oleic acid) | 35.7 % of fatty acids | ± 10% | GC-FID | EUSELI |
| LP056 | C 18:2 n-6 (Linoleic acid) | 42.2 % of fatty acids | ± 10% | GC-FID | EUSELI |
| LP056 | C 18:3 n-3 (α-Linolenic acid) | 2.0 % of fatty acids | ± 20% | GC-FID | EUSELI |
| LP056 | C 18:3 n-6 (γ-Linolenic acid) | <0.1 % of fatty acids | ± 20% | GC-FID | EUSELI |
| LP056 | C 18:4 n-3 | <0.1 % of fatty acids | ± 20% | GC-FID | EUSELI |
| LP056 | C 20:0 (Arachidic acid) | 0.1 % of fatty acids | ± 20% | GC-FID | EUSELI |
| LP056 | C 20:1 n-9 (Gadoleic acid) | 1.0 % of fatty acids | ± 20% | GC-FID | EUSELI |
| LP056 | C 20:2 n-6 | <0.1 % of fatty acids | ± 20% | GC-FID | EUSELI |
| LP056 | C 20:3 n-6 | <0.1 % of fatty acids | ± 20% | GC-FID | EUSELI |
| LP056 | C 20:3 n-3 | <0.1 % of fatty acids | ± 20% | GC-FID | EUSELI |
| LP056 | C 20:4 n-6 (Aracidonic acid) | <0.1 % of fatty acids | ± 20% | GC-FID | EUSELI |
| LP056 | C 20:4 n-3 | <0.1 % of fatty acids | ± 20% | GC-FID | EUSELI |
| LP056 | C 20:5 n-3 (EPA) | <0.1 % of fatty acids | ± 20% | GC-FID | EUSELI |
| LP056 | C 22:0 (Behenic acid) | 0.3 % of fatty acids | ± 20% | GC-FID | EUSELI |
| LP056 | C 22:1 | 0.4 % of fatty acids | ± 20% | GC-FID | EUSELI |
| LP056 | C 22:2 n-6 (Docosadienoic acid) | <0.1 % of fatty acids | ± 20% | GC-FID | EUSELI |

The laboratory/laboratories are accredited by the respective national accreditation body. Non-accredited tests are marked *.

Symbol description:
* Not accredited

AR-003 v77
1.67 130516

Uncert. Measurement uncertainty

Measurement uncertainty, unless otherwise stated, are reported as expanded uncertainty with coverage factor 2. Exceptions related to analysis performed outside Sweden may occur. Additional information can be obtained upon request.

| | | | | | |
|---|---|---|---|---|---|
| LP056 | C 22:4 n-6 | <0.1 % of fatty acids | ± 20% | GC-FID | *EUSELI* |
| LP056 | C 22:5 n-6 | <0.1 % of fatty acids | ± 20% | GC-FID | *EUSELI* |
| LP056 | C 22:5 n-3 (Docosapentaenoic acid) | <0.1 % of fatty acids | ± 20% | GC-FID | *EUSELI* |
| LP056 | C 22:6 n-3 (DHA) | <0.1 % of fatty acids | ± 20% | GC-FID | *EUSELI* |
| LP056 | C 24:0 (Lignoceric acid) | <0.1 % of fatty acids | ± 20% | GC-FID | *EUSELI* |
| LP056 | C 24:1 n-9 (Tetracosenoic acid) | <0.1 % of fatty acids | ± 20% | GC-FID | *EUSELI* |
| LP056 | Saturated fatty acids | 18.3 % of fatty acids | | GC-FID | *EUSELI* |
| LP056 | mono-unsaturated fatty acids total | 37.3 % of fatty acids | | GC-FID | *EUSELI* |
| LP056 | poly-unsaturated fatty acids total | 44.2 % of fatty acids | | GC-FID | *EUSELI* |
| LP056 | Total Fatty Acids | 99.8 % of fatty acids | | GC-FID | *EUSELI* |
| LP056 | Unidentified Compounds | 0.2 % of fatty acids | | GC-FID | *EUSELI* |
| LP056 | Fatty Acids, Sum Of Omega 6 Calc. | 42.2 % of fatty acids | | GC-FID | *EUSELI* |
| LP056 | Fatty Acids, Sum Of Omega 3 Calc. | 2.0 % of fatty acids | | GC-FID | *EUSELI* |
| LP056 | Fatty Acids, Omega6/Omega3 Ratio | 21.10 | | GC-FID | *EUSELI* |

Per-Olov Södergren, ASM

This test report has been created electronically and has been verified and authorised.

**Test was performed by**

*EUSELI* Eurofins Food & Agro Testing Sweden AB, Lidköping

The laboratory/laboratories are accredited by the respective national accreditation body. Non-accredited tests are marked *.

Symbol description:
* Not accredited

AR-003 v77
1.67 130516

Uncert: Measurement uncertainty

Measurement uncertainty, unless otherwise stated, are reported as expanded uncertainty with coverage factor 2. Exceptions related to analysis performed outside Sweden may occur. Additional information can be obtained upon request.

## Appendix B. Technical Product Data Sheet



60

TATE & LYLE

proatein® Oat Protein

PRODUCT DATA SHEET: **PrOatein® Oat Protein**

**Product Description:** PrOatein® Oat Protein from Tate & Lyle Oat Ingredients is a natural protein concentrate, prepared from oat bran and rich in oat protein. It also contains oat oil and oat maltodextrins, both of which occur naturally in the oat. PrOatein® is produced without chemicals addition or use of solvents, and contains no additives or preservatives.

**Appearance:** fine, beige coloured powder
**Odour:** characteristic of oatmeal
**Origin:** 100% Swedish oat, non-GMO

**Label declaration recommendation:** Oat protein

| **Supply specification** | **Value** | |
|---|---|---|
| Protein (N - 6,25, on dry matter) | > 50% | Typical 52-56% |
| Dry Matter | > 94% | |

| **Microbiological data** | **Value** | **Method** |
|---|---|---|
| Total plate count 30° cfu/g | <10 000 | NMKL Nr 86, 1999 |
| Enterobacteriaceae cfu/g | <10 | NMKL Nr 144, 2000 |
| S. aureus cfu/g | <20 | NMKL Nr 66, 3 edt. 1999 modified |
| Yeasts | <100 | IDF 94B: 1990 modified |
| Moulds | <100 | IDF 94B: 1990 modified |
| Salmonella | negative / 25g | NMKL nr 71, 5 edt. modified |
| E. coli cfu/g | negative | NMKL nr 125 3 edt. 1996 |

| **Nutritional Data** (Values per 100g PrOatein®, expressed on dry matter) | |
|---|---|
| Energy | 445 kcal or 1865 kJ |
| Fat | 17g |
| of which Saturates | 3g |
| Carbohydrate (oat maltodextrins) | 18g |
| of which Sugars | 0.4g |
| Fibre (oat beta-glucan soluble fibre) | 2g |
| Protein (N° 6,25) | 54g |
| Salt | <50mg |
| Sodium | <20mg |

**Minimum Order Quantity (MOQ):** 400kg

**Packaging:** 200kg big bags. 2 bags/pallet.
Bag labelling includes batch code, label declaration and best before date

**Storage and handling:** Store unopened packaging in a clean, dry, well-ventilated warehouse at ambient temperature and humidity. Store away from odorous materials

**Best Before:** 12 months after production date

Tate & Lyle Oat Ingredients, Älvåsvägen 1, 610 20 Kimstad, Sweden T: +46 11 253630 oat.info@tateandlyle.com
Tate & Lyle Oat Ingredients is a trading name of Tate & Lyle Sweden AB

# Appendix C. T&L Analytical Risk Assessment

TATE & LYLE

Risk assessment

PrOatein mycotoxins

Risk assessment for rawmaterial,oat. (See attached document)
Analysis results on finished product PrOatein

External analysis

During 2013 and 2014 finished product, PrOatein, has been sent to external laboratory, Eurofins, for analysis of mycotoxins. Mycotoxins analyzed are:
Aflatoxin
Ochratoxin
Deoxynivalenol
Zearalenone
Fumonisin
HT-2 toxin
T-2 toxin

All results has been in accordance with EU 1881.206 – setting maximum levels for certain contaminants in food stuff.

Internal analysis
Moister: max 6%

Based on risk assessmnt for rawmaterial ,oat, external and internal analysis performed on finished product, PrOatein, the overall risk has been judged as LOW.
Frequenzy of analysis on mycotoxin set to twice yearly.

Tate&Lyle Sweden AB, Kimstad
12-Dec-2014

Ingbritt Johansson
Quality Manager



62

TATE & LYLE

Risk assessment raw material

| | Potential hazard B=Biological C=Chemical P=Physical | Likelihood(L) | | Severity(S) | | Risk L x S | Overall Risk Low = 0-2 Moderate = 3-5 High = 6+ |
|---|---|---|---|---|---|---|---|
| Raw material | | Rating | Justification | Rating | Justification | | |
| Oat | C -Mycotoxins | 1 | Supplier approval.<br>Contract with supplier.<br>Raw material specification: Oat of Food Grade Mycotoxins according to EU 1881/2006 - setting maximum levels of certain contaminants in foodstuff.<br>Moister: max 14%<br>At T&L production plant stored under dry conditions in silo max 48 hours. | 3 | Mycotoxins are known carsinogens in humans | 3 | Moderate |
| | C- Pesticides | 1 | Supplier approval.<br>Contract with supplier.<br>Raw material specification: Oat of Food Grade Pesticides according to EU 1881/2006 - setting maximum levels of certain contaminants in foodstuff.<br>Dehulling of oat before milling. | 3 | Certain pesticides may have adverse side effects in humans | 3 | Moderate |
| | C- Heavy Metals | 1 | Supplier approval.<br>Contract with supplier.<br>Raw material specification: Oat of Food Grade Heavy Metals according to EU 1881/2006 - setting maximum levels of certain contaminants in foodstuff. | 3 | Heavy metals are known as health concerns in humans | 3 | Moderate |



63

# Appendix D. Stability Test Results (Batch No. 1149)

| Analysis | Start R | 3 mos. R | 3 mos. V | 3 mos. F | 6 mos. R | 6 mos. V | 6 mos. F | 9 mos. R | 9 mos. V | 9 mos. F |
|---|---|---|---|---|---|---|---|---|---|---|
| Peroxide number mekv/kg | 0.3 | x | 26 | x | 27 | 26 | 0.4 | 21 | 44 | 40 |
| Free fatty acids g/100g | 15 | x | 14.3 | x | 14 | 14 | 15 | 14.3 | 13.5 | 13.9 |
| Protein content* g/100g | 52.7 | 52.3 | 53 | 52.4 | 52.4 | 53.3 | 52.5 | 52.3 | 52.7 | 52.3 |
| Dry matter g/100g | 97.9 | 97.8 | 98 | 98.3 | 97.7 | 98.1 | 98.4 | 97.3 | 97.5 | 98.1 |
| Beta-glucan g/100g | 0.5 | 0.6 | 0.6 | 0.6 | 0.6 | 0.6 | 0.6 | 0.5 | 0.6 | 0.6 |
| Mol. wt. milj.Dalton | x | x | x | x | x | x | x | x | x | x |
| pH 10% solution | 6 | 5.7 | 5.8 | 5.8 | 6.2 | 6.2 | 6.2 | 5.7 | 5.8 | 5.8 |
| Appearance | OK | OK | DK | DK | DK | OK | OK | OK | OK | DK |
| Color | OK | OK | OK | OK | OK | DK | DK | OK | OK | OK |
| Smell | OK | OK | OK | OK | OK | OK | OK | OK | Slight rancid | OK |
| Taste | OK | OK | OK | OK | OK | OK | OK | Slight after-taste | Rancid after-taste | OK |
| Vol. wt. kg/l | | | | | | | | 0.58/0.60 | 0.59/0.60 | 0.56/0.58 |
| | | | | | | | | | | |
| Total count cfu/g | 70 | 200 | 300 | 200 | 280 | 190 | 200 | 750 | 550 | 550 |
| Total thermophilic count cfu/g | 100 | <10 | 60 | 120 | 90 | 50 | 30 | 60 | 20 | 50 |
| Enterobact. cfu/g | <10 | <10 | <10 | <10 | <10 | <10 | <10 | <10 | <10 | <10 |
| Bacillus.cereus cfu/g | 20 | <20 | <20 | 60 | 40 | <20 | <80 | 60 | 20 | 50 |
| Staph. aureus cfu/g | <20 | <20 | <20 | <20 | <20 | <20 | <20 | <20 | <20 | <20 |
| Yeast cfu/g | <20 | <20 | <20 | <20 | <20 | <20 | <20 | <20 | <20 | <20 |
| Molds cfu/g | 20 | <20 | 20 | 40 | 120 | 20 | 80 | 60 | 40 | 60 |
| E. coli cfu/g | x | x | x | x | x | x | x | x | x | x |

* R - room temperature; V - 40°C; F - freezer (0°C)

| Analysis | 12 mos. R | 12 mos. V | 12 mos. F | | 18 mos. R | 18 mos. V | 18 mos. F |
|---|---|---|---|---|---|---|---|
| Peroxide number mekv/kg | 29 | >70 | 28 | | x | x | x |
| Free fatty acids g/100g | 15 | 14 | 13 | | x | x | x |
| Protein content* g/100g | 50.8 | 50.3 | 51.9 | | 52.1 | 51.7 | 51.6 |
| Dry matter g/100g | 96.8 | 96.9 | 98.1 | | 96.5 | 97.3 | 97.9 |
| Beta-glucan g/100g | 0.7 | 0.7 | 0.6 | | 0.6 | 0.6 | 0.6 |
| Mol. wt. milj.Dalton | x | x | x | | x | x | x |
| pH 10% solution | 5.7 | 5.1 | 5.8 | | 5.7 | 5.2 | 5.7 |
| Appearance | OK | OK | OK | | OK | OK | OK |
| Color | OK | OK | OK | | OK | OK | OK |
| Smell | OK | Rancid | OK | | OK | Rancid | Slight sweet |
| Taste | Slight after-taste | Rancid | OK | | Bitter | Rancid | OK |
| Vol. wt. kg/l | 0.58/0.59 | 0.60/0.62 | 0.55/0.56 | | 0.58/0.60 | 0.61/0.63 | 0.55/0.56 |
| | | | | | | | |
| Total count cfu/g | 140 | 100 | 280 | | 50 | <50 | <50 |
| Total thermophilic count cfu/g | 60 | 500 | <50 | | <50 | <50 | 100 |
| Enterobact. cfu/g | <10 | <10 | <10 | | <10 | <10 | <10 |
| Bacillus. cereus cfu/g | 40 | <20 | <20 | | <20 | <20 | <20 |
| Staph. aureus cfu/g | <20 | <20 | <20 | | <20 | <20 | <20 |
| Yeast cfu/g | <20 | <20 | <20 | | <20 | <20 | <20 |
| Molds cfu/g | 40 | <20 | 80 | | 40 | <20 | <20 |
| E. coli cfu/g | x | x | x | | x | x | x |

- R - room temperature; V - 40°C; F - freezer (0°





65

# Exhibit I. Report of the Expert Panel

# OPINION OF AN EXPERT PANEL ON THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF OAT PROTEIN FOR USE IN FOOD

## Introduction

An independent panel of experts, qualified by scientific training and experience to evaluate the safety of food and food ingredients was requested by Tate & Lyle to determine the safety and Generally Recognized As Safe (GRAS) status of oat-derived protein PrOatein®. Oat-derived protein is intended for use as a source of protein for enrichment of foods. It will be added to foods at per serving levels in an identical fashion (technical function and amount) to those described in other GRAS Notification submissions to the U.S. FDA for other protein sources such as canola protein isolates (all received no objection letters; GRNs 327 and 386). Example food categories include bakery products; snack foods; dairy products; processed meat products; beverages, soups, and nutritional beverages; dry instant milkshake and protein drinks; instant powdered nutritional beverages; vegetarian food products and meat analogues; and meal replacement/nutritional bars. The amount used will not exceed the amount reasonably required to accomplish its intended technical effect.

A safety review based on the existing scientific literature on the safety of oat-derived protein as well as other plant-derived protein and protein isolate ingredients (through October 2014) was conducted by ToxStrategies, Inc. and is summarized in the attached dossier. The Expert Panel members reviewed the dossier prepared by ToxStrategies and other pertinent information and agreed to the conclusions described below.

## Description

Oat protein (PrOatein®) is a protein concentrate, prepared from oat bran and rich in oat protein, typically containing 52-56% protein (dry basis). It also contains oat oil and oat maltodextrins (approved in 21 CFR §184.1444) both of which occur naturally in the oat, as well as a small amount of minerals and β-glucan. The PrOatein® oil fraction (16-18% of the PrOatein® product) is comprised of approximately 42% linoleic acid, 36%, oleic acid, 16% palmitic acid, 2% α-linolenic acid, and 4% other fatty acids (C20 - C24) normally found in oats. The high concentration of unsaturated fatty acids (namely the monounsaturated oleic acid, along with the high amount of monounsaturated and polyunsaturated fatty acids (mainly omega-6) provides a desirable nutritional profile. Oat protein is also rich in essential amino acids (including leucine, isoleucine and lysine).

The Chemical Abstracts Service (CAS) Registry Number for oat proteins is 134134-87-5 and the trade name of Tate & Lyle's oat protein is PrOatein® or PrOatein® Oat Protein.

## Manufacturing Process

Tate & Lyle's PrOatein® product is manufactured in a two-step process following current Good Manufacturing Practice (cGMP) for food (21 CFR Part 110), without the use of

chemicals or solvents and it does not contain additives or preservatives. The first-step is a dry mill process in which the oat grain is dehulled (husk and most of endosperm separated) and milled to specifications. The final output of the dry milling process is oat bran, which is employed in the second processing step, a wet process. In the wet fractionation process, the oat bran is mixed with water and food use-approved enzymes from non-GMOs (genetically modified organisms) at specified temperatures. The mixture is passed through physical separation procedures and sterilized. The process output provides insoluble fiber, protein, oat oil, maltodextrin (approved in 21 CFR §184.1444), and oat soluble fiber rich in β-glucan, all of which can be supplied as dry products.

Reagents/processing aids used in the manufacture of oat protein are limited to water and the enzyme alpha-amylase, which is commonly used in food ingredient manufacturing processes. No chemical processing aids are employed in Tate & Lyle's manufacturing process. The alpha-amylase enzyme preparation employed in the process is GRAS per 21 CFR §184.1012, complies with Food Chemicals Codex specifications, and is used at levels not to exceed current good manufacturing practice.

Analytical (chemical and microbiological) results for PrOatein® confirm that the finished product meets the proposed specifications as demonstrated by the consistency of production, the lack of impurities/contaminants (e.g., heavy metals, pesticides, microbiological toxins), and its stability over an 12-month period.

**History of Use**

There is common knowledge of a long history of human consumption of oats. Oats contain the highest protein content of all the common grains (Katz, 2001). Tate & Lyle currently markets oat protein (PrOatein®) outside of the U.S. Additionally, similar oat-derived protein products are currently marketed in the U.S. (e.g., 55Oat Protein, Oat Tech, Inc.). Humans have consumed oats and the proteins from oats as well as other food sources providing protein such as meat, dairy, eggs, fruits, vegetables, grains, nuts, and seeds for centuries. Oats have been cultivated around the world for more than 2000 years. Numerous food products containing oats are currently marketed in the U.S. and around the world. In addition, there has been a global demand for less expensive proteins with good nutritional and functional properties (Ma, 1983). Oat protein has become a desirable ingredient for addition to a variety of food products as a source of dietary protein due to its protein quality, and excellent amino acid profile as compared to soy protein (Cluskey et al., 1979).

Epidemiological studies and clinical trials have consistently revealed the cardiovascular benefits of oat consumption due to its hypocholesterolemic effects. In 1997, the FDA approved a health claim for the association between oat consumption and coronary heart disease (Katz, 2001; FDA, 1997).

Protein is found throughout the body, in muscle, bone, skin, hair, and virtually every body part or tissue. At least 10,000 different proteins are found in the body. Proteins are

made up of amino acids that act as building blocks to make all types of protein. Some amino acids cannot be made by the body and therefore must be provided by the diet (i.e., essential amino acids). Around the world (but not in the U.S.), many people do not get enough protein in their diet leading to protein malnutrition, resulting in a condition known as kwashiorkor. While animal sources of protein tend to deliver all the amino acids the body requires, other plant protein sources also deliver most of the essential amino acids and have become an important source of added protein in processed food. Current plant and cereal grain sources of added protein used in food include peas, lentils, soy, canola, rice, chickpeas, beans, wheat, and potato.

FDA has established a daily reference value (DRV) for protein of 50 g/day for adults and children four or more years of age. Furthermore, Dietary Guidelines for Americans (HHS/USDA, 2005) recommend that adults eat half their grains as whole grains, which include oats and wheat. The Institute of Medicine (IOM, 2005) recommends that adults consume a minimum of 0.8 grams of protein per kilogram of body weight. IOM also set a wide range for acceptable protein intake, ranging from 10 - 35% of calories each day. In the U.S., the recommended daily allowance of protein is 46 grams/day for women over 19 years of age, and 56 grams/day for men over 19 years of age.

To date, FDA has reviewed extensive published information and data as part of GRAS notifications for animal and plant-based protein isolates and concentrates and subsequently issued "no questions letters" (e.g., GRN No. 26 (isolated wheat protein); GRN No. 37 (whey protein isolate and dairy product solids); GRN No. 168 (poultry protein); GRN No. 182 (hydrolyzed wheat gluten isolate; pea protein isolate); GRN No. 313 (beef protein); GRN No. 314 (pork protein); GRN 386 (canola protein isolate and hydrolyzed canola protein isolate); GRN No. 447 (potato protein isolates)).

**Intended Use and Intake Assessment**

The focus of this GRAS assessment is for an identical food use of oat-derived protein as previously recognized in the GRNs identified above for current grain-based protein sources such as soy, canola, pea, lentils, wheat, rice, and whey. Similarly, oat-derived protein will be used as a source of protein for enrichment of processed foods. As described in GRN No. 386 (see below) for canola protein isolate and hydrolyzed canola protein isolate, the typical uses of protein for enrichment of foods includes bakery products, snack foods, nutritional beverages such as high protein drinks and milkshakes, instant powdered nutritional beverages, vegetarian food products and meat analogues, dairy products, and meal replacements/nutritional bars.

The proposed use concentrations and variety of food uses combined with the large average daily consumption of the described foods resulted in the calculated daily intake of the protein additives being a substantial fraction of the RDA (46 grams/day for women over 19 years of age, and 56 grams/day for men over 19 years of age), and even exceeded it at the 90$^{th}$ percentile consumption. This was also the case for GRN No. 327 (cruciferin-rich canola/rapeseed protein isolate and napin-rich protein canola/rapeseed protein isolate). As Tate & Lyle's proposed oat protein is only intended to be an

alternative source of protein for current uses in food, a similar estimate of intake would be expected if oat protein was the only source of protein used in processed foods. As other GRAS notifications have stated, we do not realistically expect that the actual consumption of foods containing oat protein would result in daily consumption greater than the DRV or RDA for protein. It is reasonable to expect that most of the population's intake of protein is, and will remain, in the form of unprocessed foods including meat, poultry, fish, and legumes. As the proposed oat protein product is only one of many protein sources for use in processed foods, only the inherent conservatism of intake calculations such as those described in the aforementioned GRNs suggest the possibility of exceeding the RDA at the 90$^{th}$ percentile (FDA, 2011; FDA, 2010).

In summary, the proposed uses of PrOatein® will not result in an increase in the overall consumption of protein, but simply provide an alternative source of well-characterized protein from oats for use in food. Therefore, cumulative intake analysis is not considered necessary.

While Tate & Lyle's PrOatein® product could be added at a higher per serving level, the use of oat protein in this manner is considered to be self-limiting for technological reasons such as product texture and/or flavor profile.

**Safety Data**

There is common knowledge of a long history of human consumption of oats. Oats have been cultivated around the world for more than 2000 years. Humans have consumed oats and proteins from oats and other grains for centuries, along with proteins from many food sources such as meats, fruits, vegetables, nuts and seeds. The U.S., Germany, Russia, Canada, France, Finland, Poland, and Australia are the largest producers of oats (FDA, 2012). Numerous food products containing oats are currently marketed in the U.S. and around the world.

Oat consumption has various health benefits, such as a decreased risk of coronary heart disease and lowering of cholesterol (FDA, 1997; Davy et al., 2002; Ripsin et al. 1992). Protein is necessary for a healthy diet; the Centers for Disease Control and Prevention (CDC, 2014) recommends that adult women and men consume 46 and 56 g protein per day, respectively. Further, several protein isolates have received GRAS designation, including wheat protein, canola protein and potato protein (FDA, 1999, 2011 and 2013, respectively).

WHO (2002) reports the digestibility of protein in oatmeal as 86% and that in cereal oats as 72%. Therefore, dietary oat proteins are expected to be almost completely digested and absorbed from the upper gastrointestinal (GI) tract by the time they reach the terminal ileum. Oat proteins would be broken down by gastric juices in the stomach and proteases in the small intestine and efficiently absorbed as small peptides or amino acids. Sherman and co-workers (1919) demonstrated that proteins present in oatmeal were very efficiently utilized in the maintenance metabolism of healthy adult volunteers. This indicated that oat proteins were effectively broken down into their constituent amino

acids and small peptides that were typical of all food proteins. The known metabolism of oat proteins is a strong indicator of the safety of oat protein isolate.

Oat protein isolates have been shown to have antioxidant activity. Following proteolytic hydrolysis of food proteins, various physiological activities have been found including radical scavenging, antihypertensive, immunomodulatory, antimicrobial, mineral binding and opioide activities (Tsopmo et al., 2010). Oat consumption decreases the risk of coronary heart disease and lowers LDL cholesterol (FDA, 1997; Davy et al., 2002; WHO, 2002). Oats are considered a satisfactory source of protein, fat and energy for infants and young children (Graham et al., 1990). Dietary protein has been shown to decrease blood pressure and may decrease the risk of cardiovascular disease (WHO, 2002).

Studies of oats, oat protein, and other protein isolate sources in humans and/or animals have demonstrated its beneficial effects as well as safety. Safety studies of other protein sources (e.g., canola protein isolates) with similar amino acid profiles to oat protein have also demonstrated a lack of toxicity at high levels of consumption.

Some studies of patients with celiac disease (CD) indicate more frequent GI symptoms while consuming an oat-containing gluten-free diet (GFD) than consumption of a traditional GFD. Such symptoms are generally mild, and the appearance of flatulence and abdominal distension has previously been attributed to the increased intake of fiber from oat products (Holm et al., 2006; Pulido, 2009). In women with breast cancer, high dietary protein intakes improved survival rates (WHO, 2002).

Extremely high protein consumption may be toxic. While it has been recommended that adults not consume more than two-fold the reference dietary amount of 1.5 g protein/kg, physically active individuals on normal diets easily exceed this amount, and persons involved in body-building consume much higher levels of protein (WHO, 2002). Dietary protein can influence kidney function, and high protein diets may be linked with increased incidence of kidney stones in susceptible individuals (Martin et al., 2005; WHO, 2002).

Various *in vivo* and *in vitro* studies show different results relative to whether oats can elicit an immune response in patients with CD. In studies which showed a response, the data indicated that certain oat varieties may be immunogenic, but others are not.

Children with atopic dermatitis and farmers with allergies to grain dust may experience allergic reactions to oat proteins. These proteins can act as skin and respiratory allergens (Boussault et al., 2007; FDA, 2012).

There are conflicting data indicating whether CD patients can tolerate oats. Allergy manifestation resulting from consumption of oats and oat products has been the subject of debate. It has been alleged that oats may cause adverse effects in individuals with celiac disease. As a result, use of oats in a GFD was not allowed. However, recent evidence indicates that oats are safe for consumption by most individuals with celiac disease

(Rashid et al., 2007). Health Canada (2007) critically reviewed the scientific literature and concluded that the majority of people with celiac disease can tolerate moderate amounts of pure oats that are uncontaminated with other cereal grains such as wheat, barley and rye. In fact, pure oats may be beneficial to persons with celiac disease, as its palatability may increase patients' compliance with a GFD (Health Canada, 2007).

It should be emphatically stated that the recommended ingredient labeling for PrOatein® is "oat protein." Thus, food product ingredient lists would state the presence of an oat ingredient and individuals who wish to avoid oats consumption for any reason would be able to identify the presence of an oat-derived ingredient.

**General Recognition of the Safety of Oat Protein**

The intended use of oat protein has been determined to be safe through scientific procedures as set forth in 21 CFR§170.3(b), thus satisfying the so-called "technical" element of the GRAS determination and is based on the following:

- PrOatein® Oat Protein is manufactured consistent with current Good Manufacturing Practice (cGMP) for food (21 CFR Part 110). The raw materials used in the manufacturing process are food grade and/or approved for use as processing aids in food. No chemical processing aids are employed in the manufacturing process. The oat protein product containing approximately 52-56% protein has been characterized and meets appropriate food grade specifications found.

- There is common knowledge of a long history of human consumption of oats. Numerous food products containing oats are currently marketed in the U.S. and around world and oat protein has become a desirable ingredient for addition to a variety of food products as a source of dietary protein.

- The intended uses of PrOatein® (oat-derived protein) will provide an alternative to other dietary sources of protein as part of the total dietary protein intakes among the U.S. population.

- Epidemiological studies and clinical trials have consistently revealed the cardiovascular benefits of oat consumption from its hypocholesterolemic effects. In 1997, the FDA approved a health claim for the association between oat consumption and coronary heart disease (Katz, 2001; FDA, 1997).

- To date, FDA has reviewed extensive published information and data as part of GRAS notifications for animal and plant-based protein isolates and concentrates and subsequently issued "no questions letters" (e.g., GRN No. 26 (isolated wheat protein); GRN No. 37 (whey protein isolate and dairy product solids); GRN No. 168 (poultry protein); GRN No. 182 (hydrolyzed wheat gluten isolate; pea protein isolate); GRN No. 313 (beef protein); GRN No. 314 (pork protein); GRN No. 327 (cruciferin-rich canola/rapeseed protein isolate and napin-rich canola/rapeseed

protein isolate); GRN 386 (canola protein isolate and hydrolyzed canola protein isolate); GRN No. 447 (potato protein isolates)). Studies in both animal and humans have been evaluated, including a 90-day rat feeding study with a canola protein isolate (min. 90% protein) very similar in amino acid profile to the proposed oat protein product. No toxicity was evident at concentrations up to 20% in the diet. No recent human or animal studies raising any new safety concerns concerning protein or protein isolates and their addition to processed foods have appeared in the published literature subsequent to these evaluations.

- The publicly available scientific literature on oats, oat protein, and other plant-derived protein products and their subsequent utilization as a source of amino acids is sufficient to support the safety and GRAS status of the proposed oat protein product.

Since this safety evaluation was based on generally available and widely accepted data and information, it also satisfies the so-called "common knowledge" element of a GRAS determination.

**Conclusions of the Expert Panel**

We, the undersigned members of the Expert Panel, have individually and collectively critically reviewed the published and ancillary information pertinent to the identification, use and safety of the oat-derived PrOatein® product. We conclude that oat-derived protein produced by Tate & Lyle under the conditions described in the attached dossier and meeting Tate & Lyle specifications is safe.

We further unanimously conclude that the intended use of oat-derived protein in food, meeting the specifications described above, is Generally Recognized As Safe (GRAS) based on scientific procedures and that other experts qualified to assess the safety of foods and food additives would concur with these conclusions.

(b) (6)

Michael Carakostas, DVM, PhD
Consultant
MC Scientific Consulting LLC
St. Helena Island, SC

3/6/15
Date

(b) (6)

Carol Knight, PhD
Consultant
Knight International

3/11/15
Date

(b) (6)

Stanley M. Tarka, Jr., PhD
Consultant
Tarka Group, Inc.

07 March 2015
Date

74

SUBMISSION END